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Iodine Brachytherapy for Large Uveal Melanomas

By

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Academic Dissertation

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To my family

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III Puusaari I, Heikkonen J, Kivelä T: Effect of Radiation Dose on Ocular Complications after Iodine Brachytherapy for Large Uveal Melanoma: Empirical Data and Simulation of Collimating Plaques. *Invest Ophthalmol Vis Sci 2004; 45:3425-34.*

IV Puusaari I, Damato B, Kivelä T: Transscleral Local Resection vs. Iodine Brachytherapy for Uveal Melanomas that are Large because of Tumor Height. *Graefe's Arch Clin Exp Ophthalmol, in press*.

Abbreviations

ABS	American Brachytherapy Society
AJCC	American Joint Committee on Cancer
AL	Axial Lenght (of the eyeball)
ALT	Alanine aminitransferase (enzyme)
AP	Alkaline phosphatase (enzyme)
AST	Aspartate aminotransferase (enzyme)
BPS	Bebig Plaque Simulator
CGE	Cobalt Grey equivalent
CI	Confidence interval
CT	Computed tomography
COMS	Collaborative Ocular Melanoma Study
CRR	Competing risks regression
ERD	Extrapolated response dose
FAG	Fluorescein angiography
FNAB	Fine-needle aspiration biopsy
HR	Hazard Ratio
IBT	Iodine brachytherapy
ICG	Indocyanine green angiography
IOP	Intraocular pressure
IUCC	International Union Against Cancer
MRI	Magnetic resonance imaging
LBD	Largest basal diameter (of a tumor)
LD	Lactate dehydrogenase (enzyme)
LQ	Linear quadratic (model)
NNTB	Number needed to treat for one patient to benefit
NNTH	Number needed to treat for one patient to be harmed (e.g. by a side effect)
NVG	Neovascular glaucoma
RD	Retinal detachment
RuBT	Ruthenium brachytherapy
TNM	Tumor, Node, Metastasis (classification)
TSR	Transscleral local resection
TTT	Transpupillary thermotherapy

US	Ultrasonography
VA	Visual acuity
WHO	World Health Organization

1. Abstract

This study was undertaken to evaluate the safety and efficacy of Iodine-125 brachytherapy (IBT) as a primary treatment for large uveal melanomas. Until recently, enucleation has been the treatment of choice for large uveal melanomas in most centers. The Helsinki University Eye Hospital, a national tertiary referral center managing more than 90% of uveal melanomas in Finland, has since 1990 offered iodine brachytherapy for all patients unwilling to undergo enucleation for a large uveal melanoma.

The first aim of the study was to assess survival, local tumor recurrence and preservation of the eye and vision. The definition of a large tumor and most of the inclusion criteria were adopted from the Collaborate Ocular Melanoma Study (COMS) to facilitate comparison of results with this large, prospective multi-center study in which only enucleation was considered for large tumors. The second part of the study focused on the complications of IBT and their risk factors, and the third part used computer models to assess radiation dose delivered to key ocular structures during the treatment and the role of radiation in the development of complications and vision loss. A collimating plaque design to reduce radiation dose to healthy tissues was developed and tested using computer models. The last part of the study compared transscleral local resection (TSR) with IBT in managing the thickest large uveal melanomas, which were associated with a high risk of ocular morbidity and vision loss after IBT in the first parts of the study.

I. Kaplan-Meier estimates of all-cause and melanoma-specific survival were 62% and 65%, respectively, and visually comparable with the survival experience of patients reported by the COMS. Local recurrence developed in 6% of eyes and 84% of eyes were conserved at five years. Visual prognosis was guarded with 11% avoiding loss of 20/70 vision and 26% avoiding loss of 20/400 vision in the tumor eye at two years. Large tumor height and short distance from the posterior pole were independently associated with loss of vision.

II. Using cumulative incidence analysis to account for competing risks, such as enucleation and metastatic death, the 5-year incidence of cataract was 79%, glaucoma 60%, optic neuropathy 46%, maculopathy 52%, persistent or recurring retinal detachment (RD) 25%, and vitreous hemorrhage 36%. More than 80% of complications appeared within 3 years of treatment. In multivariate competing risks regression models, increasing tumor height was associated with cataract, iris neovascularization and RD. Maculopathy and optic neuropathy were associated with distance from the tumor to the respective structure.

III. Dose to the optic disc was independently associated with optic neuropathy and loss of vision. Optic neuropathy was rare with doses under 50 Gy. Both dose to the optic disc

and dose to the macula predicted vision loss after IBT. Simulated treatment using collimating plaques resulted in clinically meaningful reduction in both optic disc (median reduction, 30 Gy) and macular (median reduction, 36 Gy) doses as compared to the actual treatment.

IV. Patients managed with IBT for a uveal melanoma that was classified as large according to the COMS criteria because of tumor height were compared with patients with similarly-sized tumors managed with TSR in Liverpool, United Kingdom. Cumulative incidence analysis and logistic regression models revealed that while long-term preservation of 20/70 vision was rare in both treatment arms, preservation of 20/400 vision was better after TSR (32% vs. 5% at 5 years). However, local tumor recurrence was also more common after TSR than it was after IBT (Cumulative incidence 41% vs. 7% at five years, respectively).

In terms of survival, IBT seems to be a safe alternative to enucleation in managing large uveal melanomas. Local tumor control is no worse than with medium-sized tumors and the chances of avoiding secondary enucleation are good. Unfortunately, side-effects from radiotherapy with the current brachytherapy protocol are frequent, and long-term prognosis of saving reading and even ambulatory vision is consequently guarded. Because the means to manage radiation damage to the optic nerve and macula are ineffective, decreasing the dose absorbed by these critical structures should be one priority in brachytherapy planning. Even when the risk for optic neuropathy and radiation maculopathy can be decreased by improved plaques and treatment planning, persistent exudative retinal detachment, iris neovascularization and neovascular glaucoma can still cause considerable ocular morbidity and permanent loss of vision because of a large retained tumor mass after IBT.

At diagnosis patients with a large uveal melanoma can be informed of all available treatment options and the benefits and risks associated with each one. In a setting with frequent competing risks, such as early metastatic death, cumulative incidence analysis provides more realistic estimates than the Kaplan-Meier method for patient counseling. If a patient is unwilling to accept the risk of local recurrence and complications associated with IBT and TSR, enucleation can be recommended as an effective and proven treatment. On the other hand, if the patient places priority on saving vision, TSR with adjuvant ruthenium brachytherapy can be considered as an alternative to IBT for tumors that are classified large because of their height, provided the patient is fit to undergo hypotensive anesthesia and willing to accept the substantial risk of local tumor recurrence. For other types of large uveal melanoma, IBT remains an option that is safe and effective in controlling the tumor. Attention must be given to refining treatment parameters and, especially, to managing local complications.

2. Introduction

Uveal melanoma, although a rare disease, is the most common primary intraocular malignancy in adults. It is characterized by early and predominantly hematogenous dissemination outside the eye and poor prognosis if clinical metastases develop. Vision in the affected eye is threatened by both the tumor and side-effects from the treatments currently available.

Uveal melanoma develops from melanocytes of the uveal tract which consists of three anatomically distinct parts. The choroid, which is a layer of highly vascular tissue between the light-sensitive retina and hard scleral shell, the ciliary body in the anterior segment of the eye, and the iris.

Most uveal melanomas grow relatively slowly over years with no or few initial symptoms, unless the tumor is very close to the foveal area of central visual acuity. Some are detected by chance during routine eye examinations, and approximately one third reach a size categorized as large before diagnosis. Delay in diagnosis is unfortunate, because tumor size is a strong prognostic factor for both survival and conservation of vision: larger tumors are associated with a higher risk of spawning metastases and are also more likely to develop vision-threatening complications after current eye-conserving treatments.

Before the 1970s nearly all uveal melanomas were managed with enucleation. The first experimental forms of radiotherapy emerged in the 1930s and the past three decades have seen the development of several eye-conserving treatments based on both irradiation and microsurgery. Currently, the vast majority of eyes with small to medium-sized melanomas can be saved with these techniques, many with usable visual acuity. A growing body of evidence suggests no survival benefit is gained or lost with effective eye-conserving treatment compared to enucleation.

Large uveal melanomas carry a less favorable visual prognosis, and enucleation has remained the treatment of choice in most centers. Yet, when reasonable hope for saving usable vision exists or the patient refuses enucleation, several eye-conserving treatments can be considered. These include charged particle therapy, fractionated stereotactic radiotherapy, gamma knife radiosurgery, and plaque radiotherapy. Local resection is feasible for selected large uveal melanomas. However, with a plethora of frequent and different side-effects associated with each treatment, deciding which would best serve each patient can be a perplexing task for the ocular oncologist.

This study was undertaken to evaluate the safety and functional outcome of episcleral iodine plaque brachytherapy, the most common and widely available eye-conserving treatment for large uveal melanomas. A further aim was to identify the risk factors for side-effects and consequent loss of vision in order to find means to improve the functional prognosis for these patients. The first three parts of the study examine a population-based, consecutive series of patients managed with iodine brachytherapy (IBT) in a national ocular oncology center. In the fourth part, the results of IBT for a selected subgroup of these patients are compared against transscleral local resection given in another tertiary referral center for patients with similar tumors.

3. Review of Literature

3.1. Overview of Uveal Melanoma

3.1.1. Epidemiology

Uveal melanoma is the most common intraocular malignancy and the second most common melanocytic tumor in humans. The reported annual age-standardized incidence has varied from 4 to 11 per million in predominantly Caucasian populations.[32;222;274;287] In Finland (population, 5.2 million), the most recent estimate from the years 1955 to 1994 varies from 7.5 to 11 per million in males and 6.9 to 8.8 per million in females.[286] In Sweden, between 1960 and 1998, the incidence was between 8.4 and 11.7 in males and between 10.3 and 8.7 in females.[32] The incidences in both Nordic countries are higher than the 4.3 per million recently reported for the United States.[274] Male predominance has been observed in several studies,[32;222;274;287] but the reason for this remains unknown. Uveal melanoma is rare among non-Caucasians. It is estimated to be 150 times more common in Caucasian populations than in Africans and those of Oriental ethnicity.[80;182;274]

Median age at diagnosis of uveal melanoma ranges from 55 to 65,[67;80;189;222;252;274] and the disease is rare in children and teenagers.[32;273] After the age of 20 the incidence rises steadily from 0.5 per million, with steeper incline after the age of 40, to its peak at around 20 per million in the 60 to 70 years age group, after which it reaches a plateau.[164;274] The incidence of uveal melanoma has remained more or less stable over the years,[32;274] in contrast with the rising incidences of cutaneous melanoma,[84] and conjunctival melanoma.[298]

Uveal melanoma is nearly always a unilateral disease. Less than 2 uveal melanoma patients in 1000 have bilateral disease, i.e. a primary tumor in both eyes.[272] This frequency is higher than what would occur by chance, and a higher frequency of ocular melanocytosis has been noted in the patients with bilateral disease.

3.1.2. Pathogenesis

3.1.2.1. Etiology and Predisposition

Uveal melanoma arises from melanocytes of the choroid, the ciliary body and the iris (Fig.1). These cells are of neuroectodermal origin and similar to melanocytes found in the skin and the conjunctiva. However, the uveal tumors have unique characteristics not shared with melanomas occurring in other tissues. The structure of the eye, most notably the lack of

lymphatic vessels, limit the growth and dissemination of the tumor cells, resulting in characteristic growth patterns and predominantly hematogeneous dissemination.

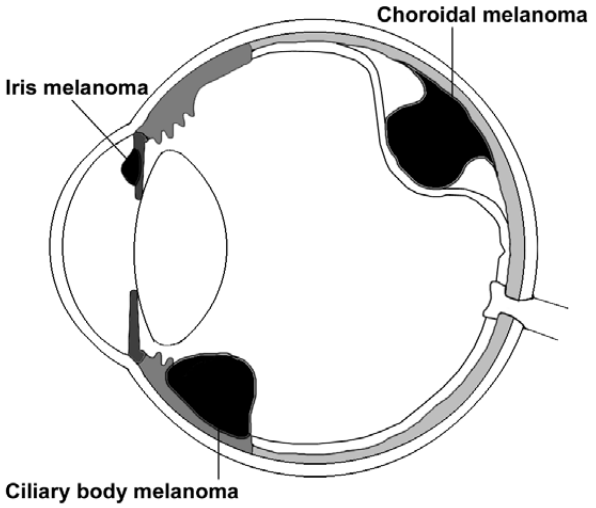

Figure 1. *Diagram of the eye showing melanomas arising from the three distinct parts of the uvea.*

It is estimated that, based on consecutive series, 64-90% of uveal melanomas originate in the choroid,[67;164;169;222] which is a highly vascular layer of tissue located between the retina and the sclera. The tumor involves the ciliary body in 24-36% of cases,[164] but no more than 10% are thought to initiate there.[169;222] A study which analyzed tumor initiation patterns in detail found it to have a predilection for the posterior pole in all quadrants.[169] Approximately 5% of tumors of choroidal or ciliary body origin extend to the iris.[169;222] Tumors initiating in the iris itself (iris melanomas) account for approximately 3% of the melanomas of the uveal tract.[145;222] These tumors differ sufficiently from ciliochoroidal tumors in terms of treatment and prognosis to be considered a separate entity.

The etiology of uveal melanoma is not known, although several potential risk factors have been studied. In addition to race and age, lightly pigmented skin and light iris color have been established as risk factors.[135;240] The role of sunlight and other ultraviolet light exposure has been documented in the etiology of cutaneous melanoma, but its association with uveal melanoma is ambiguous.[135;213;240;271] The risks associated with occupation, tobacco and hormonal factors have also been studied but no conclusive evidence has been found.[80;134;135]

Congenital ocular and oculodermal melanocytosis (nevus of Ota) is a rare pigmentary anomaly in which the number of melanocytes is increased in ocular and periocular tissues. This disorder has been associated with an increased risk for uveal melanoma.[106]

Some uveal melanomas initiate from pre-existing choroidal nevi. In a population-based study approximately one tumor in ten developed from a previously identified nevus.[86] A nevus is a relatively common finding, with a prevalence of 3-20% in a normal population.[269;318] It has been estimated that roughly 1 choroidal nevus in 9000 undergo malignant transformation into a melanoma per year.[269;318]

3.1.2.2. Genetics

Uveal melanoma is generally not considered hereditary, although some families with increased incidence have been described.[138;275] No gene responsible for the disease has been found, but studies have identified several non-random abnormalities in the genome of many uveal melanomas. The most consistent so far is the partial or total loss of chromosome 3, sometimes referred to as monosomy 3.[136] This genotype has been shown to correlate with tumor size and aggressive behavior.[218;236] Indeed, it has been suggested that uveal melanoma cells with two fully functional chromosome 3s may not develop metastasis at all. Other common chromosomal anomalies concern chromosomes 8 and 6. Extra copies or gains in chromosome 8 occur frequently together with monosomy 3 and carry an unfavorable prognosis, whereas changes in chromosome 6 are inversely related with monosomy 3 and associated with better prognosis.[268] Although it is as yet unclear whether these changes lie on the primary pathway of malignant transformation or are markers of tumor progression, their discovery is an important breakthrough opening new avenues for prognostication and further research.

3.1.2.3. Growth Patterns

Different growth patterns have been described for ciliochoroidal melanomas. When small, most uveal melanomas are flat, hardly distinguishable from benign nevi.[247;291] With time, most tumors grow along the choroid as well as in thickness resulting in a solid nodular or dome-shaped mass.[145] A diffuse variant which may involve large areas of the choroid with little increase in tumor thickness has been encountered in 3-5% of cases of posterior uveal melanoma.[96;255;293] Uveal melanoma is a slow-growing tumor. It has been estimated, based on inferred natural history of uveal melanoma, that it takes an average of 7 years for a medium-sized uveal melanoma of less than 10 mm in largest diameter to reach the large size of 15 mm in diameter.[19;187]

A uveal melanoma eventually invades neighboring tissues. As a choroidal tumor grows in height, it pushes against, weakens, and eventually ruptures through the Bruch's membrane. This herniation into the subretinal space results in the pathognomic mushroom or collar-button shape and enables the tumor to grow in height more rapidly.[146] In histological examination of eyes enucleated because of uveal melanoma, ruptured Bruch's membrane was seen in 40-87%,[145;222;293] and limited invasion of the overlying retina was documented in 26-60%.[145;293] Rarely, melanomas classified as retinoinvasive invade within the retina, cause

intravitreal seeding and infiltration of the optic nerve.[160] This type of growth occurs more frequently in eyes with pre-existing or secondary glaucoma.

The lack of Bruchs' membrane in the ciliary body causes melanomas arising there to follow a different growth pattern. The main tumor mass is often more hemispherical and can grow to compress the iris and the lens, causing secondary angle closure and cataract. A subclass of diffuse melanoma, the ring melanoma, grows circumferentially along the ciliary body making it difficult to diagnose.[74;166] The tumor can also invade the iris, the chamber angle and trabecular meshwork.

Uveal melanomas also grow outward, invading the overlying sclera, usually by growing along the vortex veins or emissary channels of the ciliary vessels and nerves. Microscopic invasion of the inner sclera is common, occurring in 50% to 80% of enucleated eyes.[145;293] In the Collaborative Ocular Melanoma Study (COMS) series of enucleated medium to large-sized tumors, tumor size was statistically associated with local invasion, with large tumors more likely to invade the retina, the vitreous and the vortex veins. Invasion of the emissary channels which occurred in approximately 56% of cases, was not related to tumor size.[293]

Macroscopic extrascleral extension, the invasion of the orbit and or conjunctiva by the tumor, has been reported in 2-17% cases of uveal melanoma.[67;145;164;245;289] Extrascleral growth has been associated with poorer prognosis,[164;208] either through direct spread along the orbital tissues and vasculature, or indirectly, as a sign of more aggressive tumor cells.

An uncommon site of intraocular invasion is the optic nerve. Invasion of the optic nerve head is reported in 2-7% of eyes with uveal melanoma.[145;293] Growth into the optic nerve is more common with juxtapapillary tumors but retinoinvasive melanomas, which have a tendency to invade non-adjacent retina and the optic nerve, have been described.[160;279;280]

3.1.2.4. Metastasis

The ability to metastasize is a characteristic of malignant tumors. Uveal melanoma metastasizes in 45% of patients within 15 years,[31;145;164;296] but individual risk is strongly influenced by several tumor and host-related factors. Remarkable features of the metastatic process of uveal melanoma are the purely hematogeneous dissemination from the primary lesion (with the exception of tumors invading the conjunctiva and accessing the lymphatic vessels there) and the overwhelming predominance of the liver as the site of metastasis. Liver is involved in more than 90% of cases of metastatic uveal melanoma and in 33-56% it is the only site of metastasis.[44;83;89;111;145;152;224;296] Other typical metastatic sites are skin, lung, bone

and brain.[44;89;152;296] Once metastases develop, the prognosis with currently available therapies is poor. One-year survival rates of 15-40% have been reported,[87;111;145] and although current treatments can slow down the metastatic growth, three year survival in recent studies does not exceed 5%.[87]

There is much we don't know about the metastatic process of uveal melanoma. One key question is when the dissemination of malignant melanoma cells outside the eye takes place.[88;103;187;292] It now seems likely, based on studies of tumor doubling times, that dissemination takes place early, even years before the primary tumor is diagnosed and treated.[48;88] Another yet unexplained feature of the metastatic uveal melanoma is the variable and often long delay before the development of clinically detectable metastases. Metastases are detected in approximately 1% of patients at the same time as the primary tumor,[307] and the incidence peaks 2-3 years later.[145;164] But in 20% of those patients who eventually develop metastatic disease, the onset is delayed more than 10 years,[164] and cases of metastases appearing more than 40 years after treatment of the primary tumor have been reported.[59;263]

3.1.3. Diagnosis

3.1.3.1. Symptoms and Signs

Uveal melanoma is usually a slow-growing tumor and the initial symptoms are often mild and unspecific. The most common initial symptoms are blurred vision (50-69%), visual field defect (9-30%) and photopsia (18-26%).[65;86;145;222] Irritation or actual pain was reported by 6-24% of patients,[86;145;222] and these symptoms usually result from ciliary body invasion or increase in intraocular pressure (IOP). Studies on the delay in diagnosis report that 60-87% of patients had symptoms at diagnosis.[65;86] In 25-30% of patients the diagnosis is made during a routine examination, when at least half of them are still asymptomatic.[65;86]

Some uveal melanomas first present through secondary effects such as glaucoma, sector cataract, vitreous hemorrhage or uveitis.[85;204;258;316] This mode of presentation is more typical for a ciliary body melanoma which can invade and occlude the chamber angle, encroach on the lens and cause hemorrhage or inflammation while remaining hidden in non-dilated fundus examination. Glaucoma secondary to uveal melanoma is more frequent with large tumors, which can cause angle occlusion either by direct infiltration or mass effect and neovascular glaucoma as the result of chronic exudative retinal detachment.[258;316]

3.1.3.2. Clinical Diagnosis

Diagnostic accuracy of uveal melanoma has improved considerably in the past 30 years. A study in 1973 reported a misdiagnosis in up to 20% of eyes enucleated because of a suspected melanoma,[259] whereas the most recent estimate by the COMS was less than 0.5%.[290] It merits notice, however, that the COMS figure is based on a data set of tumors which had a minimum height of 1 mm and minimum largest basal diameter (LBD) of 5 mm, which excludes the smallest and diagnostically most challenging lesions from the analysis. Nevertheless, the present-day ophthalmologist is better equipped for making the diagnosis with new fundusscopic examination lenses and imaging equipment such as B-scan and high-frequency ultrasound.[15;183;265] A considerable part of this success is also due to concentrating the care of uveal melanoma patients to specialized ocular oncology centers and the wealth of experience and understanding of the disease that has also become available due to meticulous research and reporting by several study centers worldwide.

The diagnosis of uveal melanoma is most often based on typical appearance of the tumor on fundus examination and B-scan ultrasound. The key clinical features are size, shape, pigmentation, exudative retinal detachment (RD) and orange lipofuscin pigment. The interior of the tumor often gives a low-reflectivity signature in B-scan ultrasonography. This examination can also detect macroscopic extrascleral extensions. Tumor edges extending anterior to ora serrata can be located using transillumination, which is also useful for detecting melanomas in the ciliary body. The latter, however, are best visualized with high-frequency ultrasound.[99;183;184] Further confirmation can be obtained with computed tomography (CT) and magnetic resonance imaging (MRI) of the orbit.[26;61;226;265;314] Especially with atypical lesions, such as amelanotic tumors which may resemble a choroidal metastasis, a systemic screening for a primary tumor elsewhere is warranted.

Fluorescein angiography (FAG) has been used to identify the double circulation pattern typical of uveal melanoma,[18;288] but is seldom needed anymore except in cases where the differential diagnosis of a vascular tumor is considered. Indocyanine green angiography (ICG), a more recent diagnostic method[254] which uses infrared light for better tissue penetration, has been shown to be superior to FAG in imaging tumor vascularization[196] and, together with confocal digital imaging techniques, can also detect microvascular patterns,[195;197] an established prognostic indicator which was previously accessible only on histopathologic examination of tumor tissue.

Fine-needle aspiration biopsy (FNAB) has been used as a means of confirming an otherwise difficult diagnosis.[25;28;54;95;183;266] The biopsy can be performed either directly through the sclera or transvitreally, under visual control. The techniques have proven to be reasonably safe and accurate, but there has been some concern that this invasive manipulation of tumor tissue might promote dissemination of malignant cells into the vitreous or outside the eye. No conclusive evidence in support of these risks have been found. With the discovery of new cytology- and genome-based prognostic factors otherwise inaccessible in eyes treated with radiotherapy, the indications for FNAB may broaden in the future.[95;183]

The challenge in the diagnosis of uveal melanoma today is rarely in differentiating it from other ocular tumors but in detecting the tumors earlier, when they are smaller. It is unknown how early these tumors should be detected and treated to prevent metastatic spread and thus improve survival, but it seems clear that early treatment of the consequently smaller tumors would increase the chances of preserving the eye and visual function.[3;86] Differentiation between benign choroidal naevus and a small malignant melanoma is often challenging. One option is to observe for growth but the safety of this practice has been questioned.[13;291;292] The clinical characteristics that predict growth of a small choroidal melanocytic lesion are the presence of symptoms, thickness over 2 mm, subretinal fluid, presence of orange lipofuscin pigment on the tumor surface, and location touching the optic disc. Features associated with benign behavior are drusen over the tumor and presence of retinal pigment epithelium changes such as hyperpigmentation over and around the tumor.[247;291]

3.1.3.3. Classification

Several classification systems for uveal melanomas have been suggested to be used as prognostic tools, to help the ocular oncologist in managing and counseling the patient, and to facilitate research and comparison of results from different centers.

In 1931, Callender published his classification system for uveal melanomas based on the morphology of tumor cells, their nuclei and arrangement.[40] Spindle A and spindle B cells are fusiform in shape and have relatively normal nuclei with small or indistinct nucleoli. The third cell type, called epithelioid, comprises larger, less differentiated cells with large nuclei and prominent nucleoli. With modifications suggested by pathologists of the Armed Forces Institute of Pathology in 1983,[186] this system, which classifies uveal melanomas as spindle, mixed, or epithelioid in the order of worsening prognosis, is still the backbone of uveal melanoma histology. However, with increasing numbers of uveal melanomas now being

managed conservatively with radiotherapy, histological samples are not routinely available for the implementation of the Callender classification in clinical practice.

Classification based on tumor size, such as the initially used Warren classification and its modifications, have been shaped by clinical conventions. A choroidal tumor less than 2-3 mm thick and under 15 mm in diameter can either be a large nevus or a small melanoma, depending on other characteristics and documented growth. Medium-sized tumors, consequently, were defined as those that are large enough to require active treatment instead of mere observation but smaller than what is considered large.[14;309]

The threshold between a medium-sized and a large uveal melanoma, especially in terms of height, shows great variation in the literature, ranging from 5 to 10 mm.[14;81;234;249;309] Some definitions of the upper limit for the medium-sized category have been based on the maximum tumor size eligible for conservative treatment at the time, resulting in increasingly large tumors being re-classified as medium-sized as eye-conserving techniques evolve. Even the COMS changed their minimum tumor height for large tumors from 8 to 10 mm mid-way through the study period.[57]

In 1993, Augsburger suggested two classifications systems that would improve upon the existing ones. In the first, the thresholds were defined to divide tumors equally between three categories, resulting in maximum height values of 5 mm and 8 mm for small and medium-sized tumors, respectively. In the other, height thresholds of 3 mm and 8 mm were found to produce maximum separation of the survival curves, increasing the value of the classification in determining prognosis.[14]

In the 1980s the COMS researchers introduced a new size classification for their prospective multi-center study. They defined small melanomas as those that are 1.0 to 3.0 mm in thickness and 5.0 to 16.0 mm in LBD.[291] Medium-sized tumors were classified as those 2.5 to 10.0 mm in height and under 16.0 mm in LBD, unless the tumor was within 2.0 mm of the optic disc, in which case the maximum height for a medium tumor was 8.0 mm.[189] COMS large tumors were those over 16.0 mm in LBD or over 8.0 or 10.0 mm in height, depending on their proximity to the optic disc.[57] Diffuse tumors, tumors with an extrascleral extension larger than 2 mm or any iris involvement as well as those with over 50% of their bulk limited to the ciliary body were considered ineligible for the study and thus left outside the classification.[57]

The Tumor, Node, Metastasis (TNM) System is an international classification developed in collaboration by the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (IUCC) to aid in the management, research and assessment of

prognosis for different forms of cancer. The TNM classification for uveal melanoma has evolved over the years and has yet to become established world wide.[276;277] The current TNM 6th Edition categories T1,T2, and T3 closely follow the COMS definitions for small, medium-sized and large, respectively.[277] Extra-ocular extension is factored in subgroups for T1 and T2 tumors while large tumors with extraocular growth are classified as T4.

3.1.4. Primary Treatment

Once the diagnosis of malignant melanoma of the uvea has been made, several management options for the primary tumor are currently available (Table 1). These include enucleation, eye-conserving surgery, different forms of radiotherapy, and thermotherapy. The primary aim of all treatments is to safely destroy the tumor, prevent metastatic spread and promote survival. Conservation of the eye, avoiding ocular morbidity and retaining vision are secondary, if important, aims.

3.1.4.1. Observation

One approach to take when faced with a uveal tumor of undetermined malignant potential is observation. When enucleation was the only alternative, this option was easily justified for slow-growing lesions.[105] Now, with great improvement in the diagnostic accuracy of uveal melanoma and the availability of several eye-conserving treatment options, observation is recommended only for small lesions which are difficult to distinguish from benign nevi, especially when the lesion is close to the fovea.[227] Because both the risk of metastatic disease and the risk of vision loss after eye-conserving treatment increase with tumor size, active treatment should be considered when the observed lesion grows or manifests other evidence-based high risk characteristics.[247;291]

3.1.4.2. Enucleation

Until the 1970s enucleation was the standard treatment for malignant melanoma of the uvea.[260;319] When alternative, eye-conserving treatment options became available over the past 30 years, enucleation has been the standard against which other options have been measured.[16;24;76] Even now, when the majority of uveal melanomas in developed countries are managed with various eye-conserving modalities, enucleation is still a common alternative, also in the leading centers, and recommended in cases when the disease has progressed beyond reasonable hope of saving the eye and useful vision.[67;261]

Table 1. *Advantages and disadvantages of currently available primary management options for large uveal melanomas.*

	Advantages	Disadvantages
Enucleation	• Low cost • Easy and safe to perform • Practically no local recurrence • Little further management needed	• Immediate loss of eye and visual function
Transscleral local resection	• Little or no radiation to critical ocular tissues • Removes necrotic tumor tissue • Markedly less neovascular glaucoma and optic neuropathy • Better preservation of visual acuity	• Comparably high risk of local recurrence • Requires hypotensive anesthesia, which is safe only for patients of good general health • Demanding for the surgeon • Further vitreoretinal procedures often necessary
Endoresection	• Theoretically same advantages as with transscleral resection but easier and safer to perform	• Little published experience yet • Risk of intravitreal seeding of tumor tissue and satellite recurrences
Brachytherapy	• Safe to perform • High eye retention rate • Low local recurrence rate	• Intermediate costs • Irradiation of healthy ocular tissues proportional to tumor height • High ocular complication rate, further treatment often necessary • Long-term retention of good VA rare • No tumor tissue available for analysis
Particle beam (He-ions and protons)	• Safe to perform • High eye retention rate • Low local recurrence rate • Sharply defined target volume can help limit radiation maculopathy and neuropathy	• Limited to few specially equipped facilities • Anterior segment complications • Further management of ocular complication often necessary • Long-term retention of good VA rare • No tumor tissue available for analysis
Gamma knife	• Safe to perform • High eye retention rate • Low local recurrence rate • Theoretically as precise as particle beam but more widely available	• In practice, dosimetric accuracy not yet as good as with particle beam • Little published experience yet

The advantages of enucleation are that it is easy to perform in any ocular surgery unit and that subsequent local tumor recurrence is practically non-existent.[295] It also provides ample tumor tissue for histopathologic analysis, which is helpful for determining the systemic prognosis of the disease and, possibly in the near future, for assigning adjuvant systemic therapy. The downside is immediate loss of the affected eye and any visual function that was left.[190]

In terms of preventing metastatic spread and thus improving survival, enucleation has not been shown to be superior to radiotherapy or to other current eye-conserving options.[2;17;77;238;239;282] In the late 1970s McLean, Zimmerman and Foster a proposed a hypothesis that by either direct manipulation of the tumorous eye or removal of beneficial immunological stimulus presented by the primary tumor, enucleation may in fact promote metastasis as compared to radiotherapy.[270;320] To address this controversy, as well as other important questions about the treatment and prognosis of uveal melanoma, the COMS was initiated. This large, randomized, multi-center study evaluated the melanoma-specific survival after iodine brachytherapy vs. enucleation of a medium-sized uveal melanoma and found no difference during a 10-year follow-up.[76] In a parallel study, the COMS also discovered that pre-enucleation irradiation of a large tumor does not offer survival benefit over enucleation alone.[57;294;295]

3.1.4.3. Local Transscleral Resection

Local transscleral resection of intraocular tumor tissue has been used to manage uveal melanomas since the early 1970s.[69;100;215;216] The surgery is technically demanding and involves dissecting a scleral flap through which the tumor and a safety margin of surrounding uvea is resected while avoiding damage to the overlying retina. In order to limit bleeding, the procedure is done under hypotensive anesthesia, which makes it unsuitable for elderly patients and others with poor general health. Furthermore, the initial published series reported high rates of local tumor recurrence.[71] Subsequent reports have shown that administering adjuvant radiotherapy, e.g. with a ruthenium-106 plaque placed over the resection area after surgery, markedly improves local control and such adjuvant therapy is currently recommended as standard.[63]

Reports of local transscleral resection show promising preservation of visual acuity even when the tumor is large enough to be associated with considerable ocular morbidity after radiotherapy.[27;67;70;158] When used in conjunction with adjuvant plaque brachytherapy, doses

to adjacent ocular tissues are small compared to those associated with irradiation of the whole tumor volume by stand-alone radiotherapy. Furthermore, by removing the intraocular tumor mass, resection may help the eye to return to a more physiological state resulting in a lower incidence of neovascular glaucoma.[27;158] The disadvantage of local resection, even with routine use of adjuvant radiotherapy, is local tumor recurrence which is more common after resection than after primary radiotherapy.[158]

3.1.4.4. Endoresection

Endoresection, as described by Damato et al,[66] was developed for peripapillary uveal melanomas in patients for whom the preservation of vision in the tumor eye is of high priority. This technique, which involves vitrectomy followed by transretinal resection of the tumor mass with a vitreous cutter, has been controversial because of the fear that the piecemeal removal of tumor tissue may lead to intraocular dissemination of viable tumor cells and increased tumor recurrence.[123] Endoresection has also been used to remove tumors first managed by primary radiotherapy in an attempt to reduce complications related to the presence of a necrotic tumor mass.[29;33]

3.1.4.5. Laser Photocoagulation and Transpupillary Thermotherapy

Laser photocoagulation was preceded by xenon arc photocoagulation and has multiple uses in general ophthalmology. It has been used as a stand-alone therapy for small uveal melanomas, as a supplementary therapy in combination with irradiation, and as additional treatment for small marginal recurrences after radiotherapy.[22;178;192;264;304] In histopathological examination of photocoagulated tumors, the necrosis caused by a single treatment session penetrates less than 1 mm into the tumor and many tumors showed only partial or no necrosis after completed therapy. Laser photocoagulation is hence considered inadequate as a stand-alone therapy even for the smallest of uveal melanomas.[7;82]

Introduced in 1995, transpupillary thermotherapy (TTT) employs an infrared diode laser, which is aimed through a dilated pupil using a large spot size of 2-3 mm and an exposure time of 1 minute.[149;150;205;206;228;251;253] This causes irreversible cellular damage at sub-coagulation level with penetration of up to 6 mm into the tumor. The peak temperature of the heated tissue is lower, 45-65°C, and it builds up more slowly than in laser photocoagulation. Laser power required to achieve the desired effect depends on tumor pigmentation. Indocyanine green (ICG) dye has been used to enhance heat build-up in lightly pigmented tumors.[72]

TTT has proven to be a well tolerated and effective treatment for retinal hemangiomas[104;225] as well as small retinoblastomas[1;177;250] but its effectiveness as a standalone treatment of uveal melanoma has been questioned. In particular, melanoma cells invading the overlying sclera may escape destruction because current TTT is unable to equally elevate the temperature of the pigmented tumor and lightly pigmented sclera. As a solution, a so-called sandwich therapy combining TTT with reduced-dose plaque brachytherapy has been investigated.[206;244] The maximum tumor height recommended for TTT alone is 4 mm whereas tumors up to 8 mm have been managed with the sandwich technique. Reported side-effects typical of TTT include branch retinal vessel obstruction and deep scotomas in areas where the nerve fiber layer of the retina has been damaged.[228;251;253;313] In terms of ocular morbidity and preservation of visual function, TTT has not been shown to offer any advantage over plaque brachytherapy.[129]

3.1.4.6. Plaque Brachytherapy

Brachytherapy is defined as radiotherapy in which the radioactive sources are placed near or within the tumor. In 1929, Moore managed a malignant uveal melanoma by surgically implanting radioactive radon seeds within the tumor tissue.[194] In the following decades, Stallard[281] and his contemporaries further developed brachytherapy of ocular tumors into its current form: concave plaques containing a radiation source, which are sutured onto the external scleral surface next to the tumor for a pre-calculated time.[210]

The tumor is localized during surgery with transillumination, indirect ophthalmoscopy with scleral indentation, or both. After peritomy, a non-active dummy plaque is first placed on the sclera to verify accurate positioning. If necessary, one or more ocular muscles are deinserted if their insertions interfere with plaque placement. Transillumination can be used to check that the plaque covers the whole tumor, usually with up to 2 mm of safety margin on all sides. Scleral sutures are then placed to fix the plaque using its suture holes and the dummy plaque is then replaced with an active one.

Several radionuclides have been used in ophthalmic brachytherapy (Table 2). The first isotope that saw general use in the treatment of uveal melanoma was cobalt-60, a high-energy isotope emitting both gamma and beta radiation and with a half-life of 5.2 years.[262] The high energy (1.3 MeV) radiation released from this isotope is not adequately blocked by the metal plaque, which causes unnecessary irradiation to orbital tissues as well as safety concerns to medical personnel administering the treatment.[144] Cobalt-60 brachytherapy also delivers more radiation to healthy ocular tissues and more radiation-related complications

Table 2. *Radionuclides used in ophthalmic brachytherapy*

Nuclide	Symbol	Type	Energy	Half-Life	Introduced*	Max Height†
Cobalt	Co-60	Gamma / Beta	1.3 MeV / 320 keV	5.2 years	1948	
Ruthenium	Ru-106	Beta	293 keV	373 days	1964	5 mm
Iodine	I-125	Gamma	27-35keV	60 days	1975	
Strontium	Sr-90	Beta	546 keV	29 years	1983	5 mm
Iridium	Ir-192	Gamma / Beta	600 keV / 370 keV	74 days	1983	
Palladium	Pd-103	Gamma	21 keV	17 days‡	1986	

* First reported period of use in ophthalmology
† Maximum tumor height that can be safely managed in one application
‡ The actual half-life of Pd-103 is 50 days but the energy emission drops dramatically after 17 days

were observed[52;211] than with low-energy gamma-emitters such as iodine-125 (27-35 keV) and palladium-103 (21 keV), which have replaced cobalt in ocular brachytherapy. Of these, iodine-125 is currently the most commonly used, and well documented in the literature.[47;76;131;143;210;212;229] Few centers use palladium-103, but available reports indicate that its lower energy may yield more favorable dose distribution and fewer complications than iodine-125.[92;93] Iridium-192 is another less often used option in brachytherapy, which resembles Cobalt-60 in that it produces both gamma and beta rays but with half the maximum energy.[120;299]

Ruthenium-106 is a beta-emitter with high energy (293 keV), and low tissue penetration. As such, it is well suited for the treatment of small and medium-sized uveal melanomas with heights of 5 mm or less. Ruthenium brachytherapy was introduced in 1964 by Lommatzsch and Vollmar and has been well documented over the past decades.[38;174;175;217;243] Strontium-90 is another beta-emitter with high activity resulting in a high dose rate and short application time. Reports suggest that strontium is as effective and at least as well tolerated as ruthenium.[193;302] A recent report also describes a bi-nuclide applicator which combines iodine with ruthenium in order to manage thicker tumors than what is possible with ruthenium alone but with a smaller dose delivered outside the target volume compared to iodine.[94]

Brachytherapy plaques are most often rounded, made of gold (iodine), platinum, or silver (ruthenium) and come in several diameters in order to effectively treat tumors of different size.[154;201;210] Some plaques have a notch for the limbus or for the optic nerve so that the plaque can be placed adjacent to these structures. Some plaques have a collimating rim in

order to limit the lateral scatter of irradiation whereas others place the seeds in individual collimating slots.[11;133] While many ocular oncology centers have adopted the COMS plaques, many others have their own plaque designs, which vary greatly in the positioning and number of radioactive seeds. In some plaques the number and position of the radioactive seeds can be adjusted to suit individual tumor shapes and to minimize irradiation of critical ocular tissues. Such an individually customized treatment plan is also known as conformal brachytherapy.[12;162;202] In the past decade, computer-based brachytherapy planning software have become available which greatly help in the accurate planning and customizing of treatment.[10;162;209]

Plaque brachytherapy is currently the most common treatment option for uveal melanoma. It offers good chances of conserving the eye, often with at least some useful vision.[49;189;212] The procedure is relatively easy and safe to perform on almost any patient and the costs are reasonable. The main disadvantage of brachytherapy is the less sharply defined intraocular dose distribution compared to charged particle radiation, which limits the ability to shield healthy ocular tissues from radiation. Risk of local recurrence is also higher than after enucleation but lower than after local resection and TTT.

3.1.4.7. Charged Particle Irradiation

Proton beam[114;117;241] and helium ion[46;47;172] irradiation, collectively known as charged particle radiation, have been used since the late 1970s as a means to destroy intraocular tumors. Both methods require the use of a cyclotron to produce the particles, which, at the end of their range, release energy through interactions with electrons in the medium. The range at and over which most of the energy is released can be controlled by modulating the energy of the particles.[109] This phenomenon is known as the Bragg peak effect which, in combination with collimators adjusting the cross-section of the particle beam, makes it possible to sharply define the three-dimensional field of radiation and place it over the tumor while sparing surrounding intraocular tissues. Accurate placement is facilitated with detailed three-dimensional computerized treatment planning and radio-opaque tantalum rings sutured onto the scleral surface.

The main advantage of charged particle radiation over brachytherapy is the more controllable intraocular dose distribution which enables all parts of the tumor to receive equal doses of radiation while sparing the radiation-sensitive vital ocular structures. In theory, this advantage becomes more pronounced with increasing tumor size.[114] The disadvantage of charged particle therapy, in addition to being limited to facilities with access to a nuclear

accelerator, is the increased incidence of anterior segment complications, such as keratoconjuctivitis sicca, loss of eyelashes, and depigmentation of skin in dark individuals.[55;140] Reports of ocular morbidity and preservation of vision comparing brachytherapy with charged particle radiation in the treatment of patients with tumors of various sizes, show no clear advantage in favor of either method,[55;139;312] although some individual patients, e.g. those with a tumor which is located adjacent to the optic disc or an awkwardly shaped tumors in the iris or ciliary body, may benefit from the more sharply limited treatment field of charged particle radiation.

3.1.4.8. Stereotactic Radiotherapy

Stereotactic radiotherapy, also called stereotactic radiosurgery, was first envisioned by Leksell in the 1960s to manage intracranial tumors. The principle is to accurately map the location and shape of the lesion in three dimensions and then direct several collimated beams of gamma radiation from multiple radiation sources to converge in that exact target volume. With the evolution in the accuracy of three-dimensional imaging, tumor volumes as small as medium to large size uveal melanomas have been managed with the Leksell Gamma Knife since the mid-90s.[181;198;199] The advantages and disadvantages are similar to those of the charged particle therapy: target volume can be relatively sharply defined to spare adjacent healthy tissues but, in spite of this, anterior segment complications such as dry eye and neovascular glaucoma are still an issue. Furthermore, for the same level of dose conformation, the stereotactic approach requires more beams to be coordinated than in charged particle radiotherapy, which results in increased treatment time, lower dose rate and more challenges in immobilizing the eye for the treatment.[311]

3.1.5. Treatment and Prognosis of a Large Uveal Melanoma

3.1.5.1. Choice of Primary Treatment

Until quite recently, most authors recommended enucleation for large uveal melanomas. This has been justified by the fear of increased local recurrence and of uncontrollable side-effects resulting from radiotherapy of large intraocular tumor volume. There is subsequent paucity in studies that systematically evaluate an eye-conservative approach for large uveal melanomas, or prospectively compare two alternative methods. There is also a lack of a universally implemented staging system for tumor size, resulting in the aforementioned variability in the definition of a large tumor.

The most important study of large uveal melanomas is undoubtedly the COMS Large Tumor Study which randomized patients for enucleation with or without pre-enucleation irradiation.[57;130;294-296] Although lacking a conservative treatment arm, the study has provided useful survival data for this group of patients. Of the conservative treatment options, stereotactic surgery,[198] plaque brachytherapy,[249] and transscleral local resection[27;158] have also been evaluated specifically for large tumors. In addition to these, studies of mainly medium-sized tumors managed with proton beams,[102] helium ions,[50;55] and plaque brachytherapy with various isotopes[97;118;119;219] have included large tumors and provided some insight into the outcome for these patients.

3.1.5.2. Local Tumor Recurrence

Local tumor recurrence, unlike disease-specific mortality, is known to depend on the primary treatment method and enucleation is still the most effective way to ensure local control. Reports comparing two eye-conserving treatments for patients with variable-sized tumors indicate less recurrence after plaque brachytherapy than local resection, and possibly less still after charged particle radiation.[27;55;312] Large tumor size and posterior location are also known risk factors for recurrence.[71;143;151;220] Local recurrence after radiotherapy has been associated with increased risk of melanoma metastasis and mortality in some studies,[79;112;128;283;305] although this association has not been strong or detectable in others.[20;143]

Studies of predominantly medium-sized tumors managed with plaque radiotherapy have reported 5-year incidences of local tumor recurrence ranging from 6% to 15%.[55;118;119;151;212;219] The COMS medium tumor study reported 10.3% risk of treatment failure at 5 years,[143] and in the few reported series consisting solely of large tumors, the respective incidence has not been higher than this, ranging from 6% to 9%.[27;158;249]

3.1.5.3. Metastasis and Survival

Uveal melanoma is a potentially fatal disease. Large tumor size is known to be associated with worse prognosis.[164;185;235] Increasing evidence suggests that dissemination of the disease outside the eye takes place years before the diagnosis of a large melanoma,[48;88] in which case the primary treatment has little effect on survival provided local control is achieved. This hypothesis is supported by several studies comparing two treatments for patients with tumors of variable size,[2;17;21;24;55] as well as by the 10-year mortality findings of the COMS large tumor study, in which the histopathologically confirmed melanoma-specific mortality was

40% and 45% in enucleation and pre-enucleation irradiation arms, respectively,[130] and 64% of patients were diagnosed as having metastasis within 6 years.[296]

A population-based study by Kujala et al of the very long term prognosis of uveal melanoma in patients managed with enucleation reported 64% and 58% melanoma-specific mortality at 15 years for a subgroup of tumors with LBD ≥16 mm using the Kaplan-Meier and cumulative incidence methods, respectively.[164] Another study, which defined a large tumor as ≥8 mm in height, reported 30% and 55% metastasis rates at 5 and 10 years, respectively, using the Kaplan-Meier method.[249]

3.1.5.4. Visual Function

One of the toughest challenges during the four-decade long history of eye-conserving treatment for uveal melanoma has been preservation of the functionality of the saved eye. Not only the disturbance caused by the intraocular tumor but also the trauma to healthy tissues resulting from surgery or radiotherapy threatens the delicate function of the eye.

Defining and reporting the visual outcome of eye-conserving therapy is not a simple task, either, and varies from one center to another. Some researchers have measured vision loss as the number of Snellen lines lost compared to baseline acuity whereas others use the loss of certain VA levels as end points for their study. The most commonly used VA levels in North American centers are 20/40 and 20/200, which correspond to low vision and legal blindness, respectively. The World Health Organization (WHO) defines low vision as 20/70 or lower and blindness (loss of ambulatory vision) as 20/400 or less.

The statistical analysis of vision loss is made more complicated still by the fortunate fact that some patients who first experience loss of a VA level subsequently regain vision – and possibly lose it again later when delayed complications set in.

Currently, the chances of preserving vision are good for small uveal melanomas located at a sufficient distance from the macula and the optic disc. What is considered sufficient distance depends on tumor thickness and the chosen treatment option. With increasing tumor size and decreasing distance to the posterior pole, the prognosis for saving the vision becomes worse.[50;60;108;173;189;284] In the COMS medium tumor study, the 5-year Kaplan-Meier estimate for loss of 20/200 vision was 43%, and the thickest tumors and those closest to the foveal avascular zone had the worst mean VA in stratified analysis.[189] In a randomized study comparing helium ion irradiation and iodine brachytherapy, the proportion of patients who had lost 20/400 vision at the last follow-up were 46.5% and 52.0%, respectively.[55] After proton beam irradiation of a large series of melanomas in one center, the

5-year incidence of loss of 20/200 VA varied from 10% in the very lowest risk group to over 90% in the highest risk group.[108] The main risk factors in that study were distance less than 2 mm from either the macula, the optic disc, or both, tumor height, visual acuity at baseline and retinal detachment. A study of large tumors, defined as thicker than 8 mm, reported that the Kaplan-Meier estimate for loss of 20/200 VA was 57% at 5 years and 89% at 10 years. Two series that compared iodine brachytherapy with local transscleral resection for large uveal melanomas noted that more than 90% of treated eyes eventually lost 20/200 acuity after brachytherapy whereas 50-60% retained this VA level at least for 5 years after TSR.[27;158]

3.1.5.5. Conservation of the Eye

Failure of the eye-conserving approach results in secondary enucleation of the tumor eye. The most common causes for enucleation after radiotherapy of a uveal melanoma are local tumor recurrence and intractable treatment complications which cause either discomfort and blindness of the tumor eye or loss of fundus visibility required for safe follow-up of the tumor.[78;108;143;256] Some centers readily enucleate, as a safety measure, eyes which have lost usable vision whereas others strive to retain all asymptomatic eyes in which the tumor has regressed satisfactorily. The difference in the indications of secondary enucleation complicates the comparison of eye retention rates between centers and introduces bias in the reported incidence of complications and local tumor recurrence: in centers where enucleation is more readily performed, incidences of complications and recurrence appear to be smaller. A recent retrospective study suggests that secondary enucleation of a blind eye after plaque brachytherapy is unlikely to improve melanoma-specific survival.[20]

In the COMS medium tumor study, the 5-year Kaplan-Meier estimate for eye retention was 87.5%,[143] and in a large retrospective analysis of tumors of all sizes managed with a multimodality approach in a single center the rate was 88.9%.[67] A prospective randomized study comparing iodine brachytherapy and helium ion radiation reported 5-year ocular retention rates of 82.7% and 90.7%, respectively.[55] Ocular retention rates similar to these have been reported for other series of mainly medium-sized tumors, with comparable results after brachytherapy and charged particle irradiation.[108;119;312] In the few series consisting of large uveal melanomas and in high-risk patient subgroups of series with variable tumor size, 5-year ocular preservation rates as low as 75% have been noted.[102;108;249]

3.2. Radiotherapy of Uveal Melanoma

3.2.1. Biological Effects of Radiotherapy

The effect of any ionizing radiation, whether alpha, beta, gamma, or charged particles, on living cells is caused by disruption of the DNA strands of the chromosomes, resulting in dysfunction of reading the genetic code and of producing key proteins, and ultimately, if the damage is severe enough, in cell death. The radiosensitivity of different cell types and subsequently of different tissues varies considerably because of differences in cell cycling rates and capacity to repair damaged DNA. In general, tissues with rapidly reproducing cells such as intestinal mucosa and hematopoietic tissue in bone marrow are the most sensitive and cells with little or no reproductive capacity such as nerve cells and retinal photoreceptors are less sensitive. Even the least sensitive tissues are, however, subject to radiation damage because their blood supply is dependent on vascular endothelial cells of nearby vessels, which are relatively sensitive to radiation. Tumors also vary greatly in their ability to withstand radiation damage, with uveal melanoma being, unfortunately, one of the least sensitive. It has also been shown that different lines of uveal melanoma cells differ in sensitivity to radiation.[156;278;301]

3.2.2. Dose and Dose Rate

The unit of absorbed dose of radiation is 1 Gray (Gy), which equals 1 Joule per 1 kilogram. In brachytherapy this dose is delivered during a precalculated, continuous time period whereas charged particle radiation is usually given in several fractions, the total dose of which is measured in cobalt-Grey equivalents (CGE = proton dose in Gy * radiobiological effectiveness, 1.1 for protons and 1.3 for helium ions). In brachytherapy, the dose delivered to a certain point within the eye during a certain treatment period is directly proportional to its depth or the distance from the radioactive plaque. Hence, in brachytherapy, the sclera and tumor base receive many times the dose prescribed to tumor apex, and this difference increases with increasing tumor height. In contrast, charged particle radiation delivers a more or less uniform dose to all of the tumor mass.

The smallest dose guaranteed to kill uveal melanoma cells in vivo is not known. Stallard selected a dose of 100 Gy prescribed to the apex of the tumor,[281] after which others have reported series managed with smaller apical doses, ranging between 70 and 85 Gy.[97;210;220;231;267] The COMS medium tumor study used I-125 brachytherapy with

prescription dose of 85 Gy to the tumor apex if the tumor was more than 5 mm in height or, in the case of smaller tumors, 85 Gy prescribed to depth of 5 mm,[189] a guideline also endorsed by the American Brachytherapy Association (ABS).[201] The COMS later reported an association between lower apical dose and local failure within that dose range.[143] Gragoudas et al reported a randomized series of uveal melanomas managed with lowered-dose proton beam irradiation of 50 CGE. During the 5-year follow-up they observed no ill effects in terms of recurrence and metastasis nor a clear improvement in avoiding complications and ocular morbidity.[115] In the treatment of skin melanomas, doses lower than 50 Gy have been associated with a considerable risk of local failure.[207]

In addition to total dose delivered to the tumor, the rate at which it is delivered has an effect on the biological effectiveness of the treatment. This is because the DNA strand has two chains, one or both of which can be severed by a strike from an ionizing particle. If both are severed in a single hit, the molecule is inactivated immediately. If only one strand is severed, the result depends on whether the cell can repair this sub-lethal damage before a second hit takes out the remaining strand, and here the frequency at which these hits occur becomes a factor. The combination of single-hit and sub-lethal damage to tumor tissue can be successfully approximated with a mathematical model called the linear-quadratic (LQ) equation. The dose rate range at which the dose rate effect can be observed ranges from 10 to 1000 cGy/h. At higher dose rates, no additional biological effectiveness is achieved whereas at lower dose rates the repair of sub-lethal damage catches up with the damage caused, leading to steady-state systems in which linear dose-dependent single-hit damage predominates.[125] Tissues also differ in their capacity to repair the sub-lethal damage, which can be taken into account in the model by using appropriate α/β-ratios determined empirically.[233;300] On this basis, tissues are divided into early-reacting, which are more capable of repairing sub-lethal damage and late-reacting, which are thought to be more susceptible to higher dose rates.[126]

The relevance of the dose rate effect in the management of uveal melanoma is two-fold. In theory, treatment given with a higher dose rate is more likely to completely destroy the tumor and should improve local control, as has been observed in both animal[315] and clinical[219] studies. However, the late-reacting normal tissues of the eye are likely to be even more sensitive to the increased dose rate, which results in more ocular morbidity, which has also been noted in several studies.[6;36;119;148;219;315]

The optimal dose rate for the treatment of uveal melanoma is yet to be defined. The COMS brachytherapy protocol allows dose rates from 42 to 105 cGy/h at the tumor apex,[189]

whereas the current ABS recommendations suggest a dose rate between 60 to 105 cGy/h. An apical dose rate less than 70 cGy/h was associated with an 8-fold increase in the incidence of local tumor recurrence as compared to tumors that received this dose rate level in a study of 150 small to medium-sized melanomas.[219] On the other hand, series with lower or more variable dose rate ranges have also shown adequate local tumor control.[97;148;249;267]

3.2.3. Ocular Complications of Radiotherapy

3.2.3.1. Cataract

The sensitivity of the crystalline lens to ionizing radiation is well documented.[113;132;161;179;188;233;285] The onset and degree of lens opacity developing after radiotherapy have both been shown to be dose-dependent with a maximum tolerated threshold dose around 10-16 Gy.[113;132;191] The incidence of cataract after radiotherapy of a uveal melanoma depends on the size and location of the tumor as well as the source of radiation used. With charged particle radiation, the incidence is strongly associated to the extent to which the lens is located in the path of the particle beam,[51;113;188] whereas greater height and a more anterior location of the tumor are risk factors for cataract after plaque brachytherapy.[90;161;285]

Char et al reported significant cataract in 22% and 25% of patients with mainly posterior melanomas of variable size, randomized for iodine-125 brachytherapy and helium ion radiation, respectively.[55] Incidences from 48% to 86% have been reported for data sets with anterior[90;91;118] and large tumors.[249] Reports of cataract extraction after radiotherapy of a uveal melanoma indicate it to be a safe procedure.[110;220;306]

3.2.3.2. Iris Neovascularization and Neovascular Glaucoma

Unlike cataract, neovascular glaucoma (NVG) often causes profound and irreversible loss of vision. This complication can also cause intractable pain in the blinded eye and require a secondary enucleation.[78;256] The mechanisms leading to iris neovascularization and subsequent NVG after radiotherapy of a uveal melanoma are not fully understood. Evidence suggests that large tumor size, anterior location of the tumor,[75;78;98;117;155;172] and chronic retinal detachment[98] are associated with a higher risk for this complication.

A considerably higher incidence of NVG was noted after brachytherapy of melanomas of similar characteristics compared to local resection[27;158] which indicates that either radiation damage or the presence of the necrotic tumor mass, or both, are associated

with neovascularization. The form in which radiotherapy is administered may also have an effect. In a randomized study of posterior melanomas, NVG occurred in 29% of patients after helium ion radiotherapy and 11% after iodine brachytherapy.[55] A similar difference of 2.1% vs. 5.7% has been reported in a different data set comparing iodine brachytherapy with proton beam irradiation, respectively.[312] Size appears to be the strongest predictor with incidences of up to 33-48% reported after iodine brachytherapy of large-sized tumors.[27;158]

Glaucoma can also develop in untreated eyes with uveal melanoma.[42] In 1963, Jensen reported glaucoma of any type in 36% of the 202 uveal melanoma patients in his data set and that glaucoma was associated with tumor size and retinal detachment.[258] In 1987, Shields et al reported a lower incidence of 3% in their data set of 2111 melanoma patients, and that the leading type of pre-treatment glaucoma in choroidal melanomas was neovascular.[258]

Neovascular glaucoma can be managed with medication or by cyclophoto-coagulation,[142] but filtration surgery is generally not recommended for an eye with a uveal melanoma. Panretinal photocoagulation has been suggested both as a preventive measure and treatment.[23;108;117;155] Nevertheless, NVG is the leading cause of secondary enucleation of eyes in which successful local control was achieved with radiotherapy.[78;108;200;256]

3.2.3.3. Radiation Retinopathy

Radiation retinopathy is not uncommon after radiotherapy of posterior uveal melanomas and is a potential cause of severe vision loss.[90;116;120;122;249] Some degree of macular damage has been observed in up to 89% of patients with paramacular tumors.[122] Retina directly over the tumor and thus inside the 100% isodose volume usually undergoes total atrophy.[163;232] The clinical picture of radiation retinopathy outside the treated area includes macular edema, intraretinal microvascular abnormalities (IRMA) and capillary non-perfusion.[8;37;122] These changes have been confirmed in histopathological studies[8] and are similar to those observed in diabetic retinopathy, particularly ischemic maculopathy.

An association between radiation dose to the posterior pole and radiation retinopathy has been documented.[90;116;120;308] Gragoudas et al noted that any exposure was associated with increased risk of this complication after proton beam radiotherapy, and that above 40 Gy the risk no longer increased with increasing dose.[116] The risk of retinopathy thus exists with any radiotherapy but should be lower for patients with more anterior tumors[90;120] and for tumors small enough to be managed with Ru-106 and located further than 2-3 mm from the macula.[285] On the other hand, patients with diabetes seem to be at higher risk for this

complication, possibly due to already compromised retinal vasculature.[8;116;303] Although some degree of spontaneous repair of radiation damage to retinal vasculature is known to take place, and laser photocoagulation alone or in combination with intravitreal triamsinolone have been investigated as a therapy for radiation retinopathy,[141;157;248] long-term improvement of vision has not been documented.

3.2.3.4. Radiation Optic Neuropathy

Like radiation retinopathy, radiation optic neuropathy is a known complication of radiotherapy of a posterior uveal melanoma and capable of causing profound and irreversible loss of vision.[36;73;116;153;176] The risk has been associated with radiation dose to the optic nerve, and clinical studies have suggested a tolerance threshold between 30 and 50 Gy.[116;147;167;176] Not surprisingly, tumors directly adjacent to the optic nerve are associated with high (52-66%) probability of developing severe optic neuropathy after plaque brachytherapy,[73;176] with partial optic atrophy reported in 82% after 10 years.[176] A risk approaching 100% was reported after proton beam irradiation when the optic nerve received the full therapeutic dose of 70 CGE.[116] The risk is considerably smaller for anterior tumors. No practical treatment for radiation injury of the optic nerve is currently available. Anecdotal reports exist of the benefits of hyperbaric oxygen, if administered within days of the onset of neuropathy.[34;121]

3.2.3.5. Retinal Detachment

Some degree of exudative retinal detachment (RD) is detected in up to 75% of patients at the diagnosis of uveal melanoma.[159;317] The COMS reported RD at diagnosis in 56% and 81% of patients in their medium and large tumor studies, respectively.[57;189] The detachment often resolves in the first 6 months following radiotherapy, although in some cases it may temporarily increase possibly due to inflammation in the irradiated tumor or vascular damage.[127] Persisting or recurring RD after radiotherapy is a threat to visual function and may require secondary enucleation either by causing loss of fundus visibility required for safe follow-up of the tumor or by contributing to the development of neovascular glaucoma.[78;98;143] Persisting or progressing exudative RD is also linked to activity of a residual tumor.[35;105;127;257] The exact mechanisms causing exudative RD postoperatively are not yet understood. The complication is strongly associated with tumor size, posterior location, and also with presence of microvascular loops and networks.[145;159] It has been suggested that tumor size may be a surrogate variable representing a more dense and complex vascular system[58] as well as the disturbance caused to normal choriocapillaris by a large tumor.

The means to treat persistent exudative RD after radiotherapy are limited. According to one case report, a progressive exudative RD after Ru-106 brachytherapy successfully resolved after vitrectomy and drainage of subretinal fluid,[221] but concerns exist about the safety of posterior segment surgery in eyes with uveal melanomas. A small series of planned laser-induced hypertermia in conjunction with proton beam therapy indicated a more rapid resolution of RD than proton radiation alone,[45] whereas another report suggested endoresection after radiotherapy to limit the problems arising from the necrotic tumor mass.[29]

3.2.3.6. Vitreous Hemorrhage

Vitreous hemorrhage is detected in 3-9% of eyes at the diagnosis of a uveal melanoma.[57;101;145] This complication is linked to the perforation of the Bruchs' membrane, which often results in the typical mushroom or collar-button shape and subsequent invasion and erosion of the overlying retina.[119;145;146] Bleeding from the dying tumor after radiotherapy, if severe, can complicate the safe monitoring of tumor regression and warrant secondary enucleation. Post-radiation vitreous hemorrhage has been reported in 9-29% of patients managed with various forms of radiotherapy,[55;118;119;212;220;285] with the lowest incidence in a series of anterior tumors with ciliary body involvement. In a randomized study, vitreous hemorrhage occurred in 29.6% and 19.8% after iodine brachytherapy and helium ion radiation, respectively; the difference was not statistically significant.[55] Vitreous hemorrage is seldom the sole or the most vision-limiting complication present in irradiated eyes. Although clearing the vitreous by vitrectomy in such cases is possible, little evidence of the usefulness or safety of such a procedure in eyes with a malignant melanoma exists.

3.2.3.7. Complications of the Ocular Adnexa

Dry eye, depigmentation of the eyelid skin, punctal occlusion leading to epiphora, and loss of eyelashes have been described after particle beam and other external radiotherapy of uveal melanoma.[39;55;139;179] These complications are rare or non-existent with plaque brachytherapy[55;91] and can often be limited by careful treatment planning in particle beam therapy as well.[139]

Disturbances of ocular motility and muscle balance have been described after plaque brachytherapy, resulting from tissue trauma, muscle disinsertion and low post-treatment visual acuity.[165;242] These disturbances manifest most often as exo- or hypertropia, rarely result in long-term diplopia, but can cause cosmetic concern.

4. Aims of the Present Study

The aim of this study was to evaluate the safety, efficacy and tolerability of iodine-125 episcleral plaque brachytherapy (IBT) as a primary treatment for a population-based, consecutive group of patients with uveal melanomas that were large by the Collaborative Ocular Melanoma Study (COMS) criteria. The study was designed to assess:

- Safety, in terms of survival and local tumor control. (I)

- Efficacy in conserving the tumor eye with normal cosmetic appearance and retaining useful vision. (I)

- The incidence of side-effects and their independent risk factors. (II)

- The role of radiation dose and dose rate delivered to intraocular tissues in the development of side-effects and loss of vision. (III)

- Potential for improving the outcome for these patients by
  a) shielding intraocular structures from scattered radiation (III)
  b) managing patients whose tumors are classified large because of their height with transscleral local resection instead of IBT (IV).

5. Patients and Methods

5.1. Eligibility Criteria and Enrolment

5.1.1. Studies I-III

Eligible to these studies were patients who were diagnosed with a uveal melanoma that met the COMS criteria of a large tumor (largest basal diameter [LBD] >16.0 mm and height >2.0 mm, height >10.0 mm regardless of LBD, or a peripapillary tumor >8.0 mm by height and located <2.0 mm of the optic disc)[57] and managed with primary iodine-125 plaque brachytherapy (IBT). The LBD and tumor location were determined primarily by indirect ophtalmoscopy, B-scan ultrasonography and, in selected cases, CT or MRI. Tumor height was based on A- and B-scan ultrasonography.

Analogous to COMS, the patient was ineligible if the tumor involved the iris, if more than 50% of it was located in the ciliary body, if it was diffuse, ring or multifocal in type, or if it had an extrascleral extension of 2.0 mm or more. Also ineligible were patients who had had other treatment for their uveal melanoma before IBT. To enhance generalizability, patients were not considered ineligible if they had a history of other coexisting disease that threatened survival, another cancer or metastatic melanoma at the time of diagnosis, provided that treatment was otherwise indicated.

The study period began on November 1, 1990, and ended on June 1, 2001. The files of the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Central Hospital, a tertiary referral center which managed 90% of uveal melanomas in Finland during the study period, were reviewed. Within the period a total of 123 patients with a large uveal melanoma were identified, of whom 26 were managed by methods other than IBT: 13 with cobalt and ruthenium brachytherapy at a time when indications for IBT were evolving, one with proton beams (in Clatterbridge, UK), and 12 with primary enucleation. One patient requested primary enucleation, four tumors could not be covered with the largest brachytherapy plaque, three had caused extensive retinal detachment and iris neovascularization, which indicated poor prognosis for saving the eye, and two had caused a hemorrhagic choroidal detachment with or without subretinal hemorrhage, which made it impossible to place the plaque accurately and also greatly worsened the prognosis for saving the eye. One elderly patient initially refused treatment, and the eye was enucleated after the tumor had extended outside the globe. Consequently, 97 of the 123 patients underwent IBT as

primary treatment for a large uveal melanoma and were enrolled (Fig.2). One of them had an extrascleral extension noted at the time of plaque insertion, and enucleation was performed instead. In accordance with the intention-to-treat principle this patient was included in the Study I but excluded from Studies II-III, which focused on the effects of radiation and used per protocol analyses (Fig.2).

5.1.2. Study IV

Eligible to the study were patients with a uveal melanoma that met the COMS criteria of a large tumor solely because of tumor height (LBD 16.0 mm and height >10.0 mm or >8.0 mm if the tumor was peripapillary),[57] managed with either TSR by a single surgeon or with IBT. The accrual period was from November 1, 1990 to June 1, 2003. TSR was performed at the St. Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom, and IBT at the Department of Ophthalmology, Helsinki University Central Hospital, Helsinki, Finland. Other criteria were similar to Studies I-III.

In Helsinki, 31 new cases of large uveal melanoma were diagnosed after the accrual

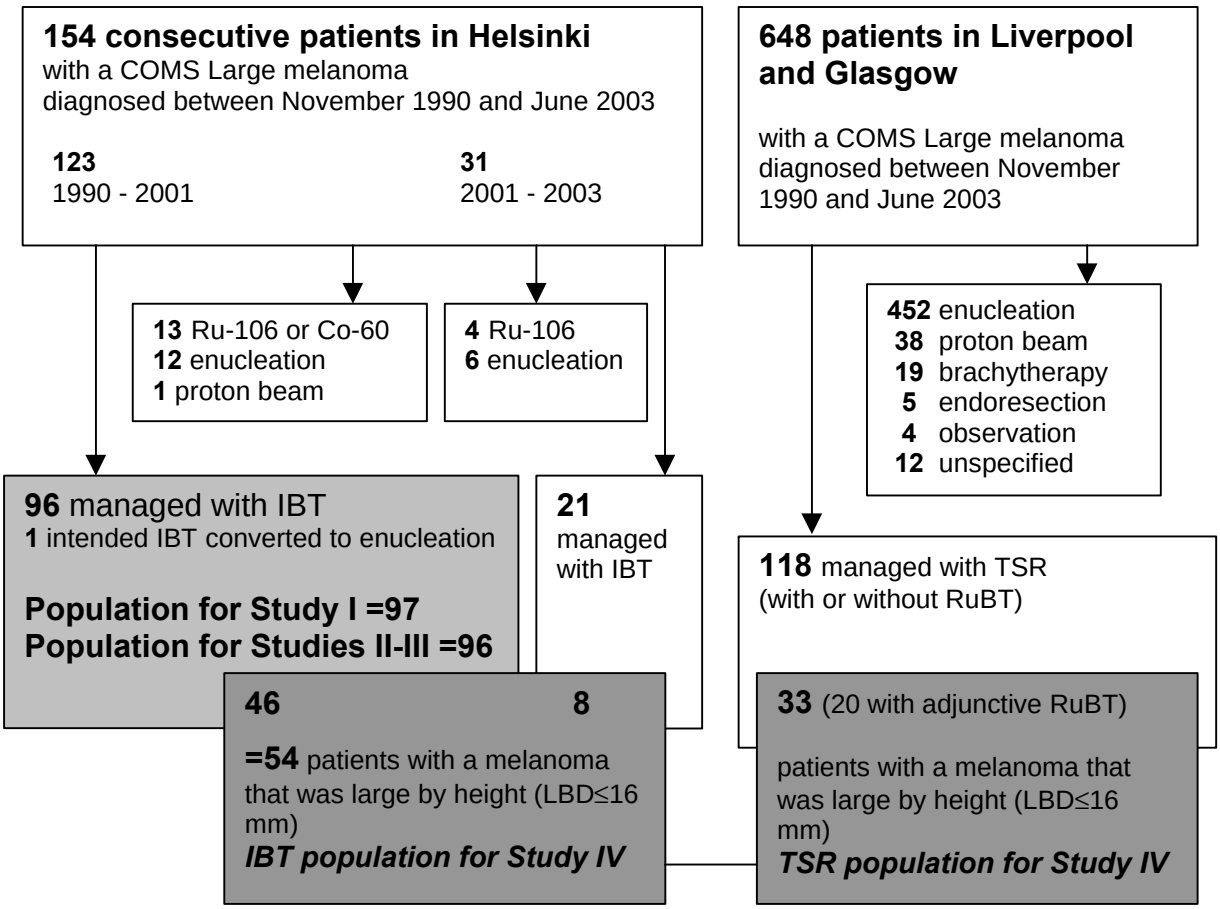

Figure 2. *Diagram of the patient populations in the four parts of the study as well as the number of the patients managed by means other than iodine brachytherapy (IBT) and transscleral local resection (TSR) in the study centers during the study period.*

period of the first three studies: 21 managed with IBT, four with ruthenium brachytherapy (RuBT) and six with primary enucleation. Of the 118 patients managed with IBT, 54 met the criteria for Study IV and were enrolled. In the UK, 118 patients with a COMS large melanoma were managed with TSR during this period, of which 33 met the study criteria (Fig.2).

5.2. Elements of Informed Consent

The first Finnish patients in this study were managed with IBT because they refused primary enucleation. Encouraged by the outcome, ocular oncologists in Helsinki subsequently informed all patients with a large uveal melanoma, in accordance with the Act of Patients' Rights (1992/785), that two treatments were available: primary enucleation and IBT, followed by secondary enucleation should a local recurrence or intractable complications from irradiation develop. The patients were then informed that local recurrence after enucleation was unlikely, whereas local recurrence and secondary enucleation were expected at least 10% and 20% of the time after IBT, respectively, based on data for medium-sized melanomas,[57;73;212;220] and that neither treatment was expected to give any significant advantage in preventing metastasis and improving survival as compared to the other.

Enucleation was recommended if the patient had a ring melanoma, a melanoma larger than the largest brachytherapy plaque, an extrascleral tumor extension over 2 mm, a tumor that grew around the optic disc or a tumor that was associated with a complication such as suprachoroidal bleeding or extensive retinal detachment, vitreous hemorrhage or iris neovascularization, which are associated with poor visual prognosis. Otherwise, the patients were managed according to their personal preference after informed consent was obtained.

In Study IV, TSR was not performed on tumors larger than 16 mm in diameter, those with retinal perforation, or on patients who were unfit for hypotensive anesthesia because of e.g. uncontrolled hypertension, liver or renal disease, cerebrovascular disease or ischaemic heart disease. TSR was usually not recommended if vision was already poor at diagnosis. The main alternatives for managing large tumors were enucleation and proton beam therapy.

If a local recurrence developed, secondary enucleation was recommended and patients who refused were managed with reirradiation. Also, if visibility to the fundus was lost, the patient was offered secondary enucleation as a safety measure. Most patients in the Finnish study populations elected to continue follow-up with ultrasonography, CT and MRI, whereas secondary enucleation was more readily recommended and performed to the TSR patients of Study IV.

The Studies followed the tenets of the Declaration of Helsinki.

5.3. Primary Treatment

5.3.1. Iodine Brachytherapy (I-IV)

Iodine-125 applicators were crafted in 1991 by a goldsmith to conform with the shape of ruthenium-106 plaques already in use.[131] Four 0.5 mm-thick unrimmed, non-collimating plaques were used: CCB (diameter 20 mm, circular, 10 seeds), CCC (Fig.1A; 25 mm, circular, 12 seeds), COB (20 mm, notch for the optic nerve, 9 seeds) and CIB (diameter 20 mm, notch for the limbus, 8 seeds). Seeds were attached with silicone rubber (RTV 3140; Dow Corning, Midland, MI) that increased plaque thickness to 1.0-1.5 mm. The first treatments of the series used either 10 mCi or 15 mCi seeds (model 6702; Mediphysics, Arlington Heights, IL) but since August 1994, 15 mCi was the standard seed intensity.

The dose to tumor apex was calculated at the time of the treatment with commercial brachytherapy software (Cadplan, Varian Dosetek, Helsinki, Finland). The angular and distance dependence dose rates were determined from tabulated correction matrices that included absorption and scatter correlations.[131;171;310] In 1995, the software was modified according to American Association of Physicists in Medicine Radiation Therapy Committee Task Group No.43.[203]

The prescription point was tumor height plus 1 mm for the sclera. Prescription dose was initially 100 Gy, and 80 Gy if the tumor was very thick in an effort to limit complications. Since 1997, the prescription dose has been 80 Gy to the apex, and very thick tumors have received a prescription dose of 70 to 60 Gy. Treatment time was calculated from the central axis depth dose curve. Seeds were replaced when the times approached two weeks. Some treatments taking place just before receiving a fresh batch of seeds were carried out loading the plaque with additional seeds from the old batch to shorten treatment time. Three patients had treatment times in excess of 450 hours when delivery of seeds was delayed.

The tumor was localized with transillumination using a fiberoptic probe, indirect ophthalmoscopy with scleral indentation, or both. A minimum safety margin of 2 mm around the tumor was desirable, but not an absolute requirement. Tumors close to the optic disc and macula were often irradiated with a smaller or no safety margin toward these structures.

Six patients received brachytherapy more than once. Three of these treatments were planned continuation to, and took place within 12 weeks of, primary IBT, in order to cover an exceptionally large or inconveniently shaped tumor. The remaining three brachytherapies were secondary treatments warranted by local tumor recurrences. The former were delivered

with two ruthenium-106 (CCB and CCC) and one iodine-125 plaque (CCB), whereas the recurrences were treated with iodine plaques.

5.3.2. Local Transcleral Resection (IV)

The techniques used for transscleral local resection have evolved over time.[63;70] The resections were performed by the same surgeon (Damato) and under hypotensive anesthesia to minimize hemorrhage. A partial-thickness scleral flap was prepared around the tumor, which was resected together with the deep scleral lamella and a safety margin of surrounding normal choroid, if possible. Adjunctive ruthenium-106 brachytherapy (RuBT; 100 Gy to 2-3 mm) was administered after surgery to 20 patients, all but one of them treated after 1995.

5.4. Data Collection

5.4.1 Baseline Evaluation (I-IV)

The diagnosis of uveal melanoma was based on clinical, ultrasonographic and, in selected cases, fluorescein angiographic findings. The clinical parameters recorded at baseline included tumor height and largest basal diameter (LBD), best corrected visual acuity (VA), and intraocular pressure (IOP). Biomicroscopy using a +90.0 diopter convex lens (Volk Optical Inc, Mentor, OH) and indirect ophthalmoscopy were performed to localize the tumor margins, to evaluate its growth pattern, exudative retinal detachment and vitreous hemorrhage, and to estimate distance from the posterior tumor margin to the optic disc and foveola. Gonioscopy was used to determine the anterior border of the tumor and to detect neovascularization of the iris, chamber angle, or both.

Liver function tests (AST, ALT, AP and LD), a chest radiogram and an abdominal ultrasonography were obtained to detect metastases. In the case of amelanotic and otherwise atypical tumors, mammography and whole body CT scans were ordered to exclude intraocular metastasis and a primary malignancy elsewhere. One patient had metastases from uveal melanoma at baseline and received IBT as a palliative treatment.

5.4.2. Clinical Follow-up

Patients were prospectively followed at 3, 6 and 12 months after brachytherapy and twice a year thereafter for 3 years, and then at least once a year, often in a regional hospital. The TSR patients were followed in a similar manner but reporting from the regional hospitals to the study center was less routine in the UK than in Finland.

Liver function tests, chest radiograph, and abdominal ultrasonography were performed annually to screen for metastasis. In selected cases, they were also performed at 6 and 18 months after treatment. All follow-up data were prospectively collected into dedicated computerized databases at both study centers.

5.4.3. Assessment of Local Tumor Control

Biomicroscopy, diascleral transillumination, indirect ophthalmoscopy, B-scan ultrasonography and, in selected cases, CT and MRI were used to assess tumor control. Recurrence was coded as vertical, marginal, ring melanoma or extrascleral.[128] An unequivocal change of 1.0 mm or more in either dimension indicated local marginal or vertical recurrence, respectively.

5.4.5. Assessment of Survival and Metastatic Status (I)

Survival status was classified as alive with or without metastasis, dead of metastatic melanoma, other cancer and nonneoplastic causes, and unknown. Death certificates were obtained from Statistics Finland and charts relating to terminal illness were retrieved. The cause of death was coded as diagnostic of melanoma metastasis if histopathologic diagnosis was confirmed in our laboratory by immunohistochemistry or, if the specimen was unavailable, the original histopathology report documented unequivocal melanin. Otherwise the cause of death was coded consistent with metastatic melanoma if based on histopathology. Patients without histopathology who had evidence of metastasis and progressive course with no evidence of a second cancer were considered to have suspected melanoma metastasis.[296]

Death due to other cancer necessitated histopathologic diagnosis. Death due to a nonneoplastic cause was classified as certain only if an autopsy had been performed. Otherwise it was required that the patient had no evidence of metastatic disease at the last review, performed no more than six months before death.

5.4.6. Assessment of Visual Acuity (I-IV)

Visual acuity was measured using the Snellen chart using the patient's own optical correction or pinhole if the vision was reduced. VA worse than 20/400 was recorded as counting fingers, hand movement, light perception and no light perception.

5.4.7. Assessment of Complications (II-IV)

Time to the following outcomes was assessed from a computerized tumor registry:

1. Progression of lens opacity, typically initially posterior subcapsular cataract in type, which decreased or would have decreased visual acuity if vision was reduced because of other reasons, evaluated by slit lamp biomicroscopy.

2. Neovascularization of the iris, chamber angle or both, evaluated by slit lamp biomicroscopy and, if suspicious vessels were seen or IOP was elevated, by gonioscopy.

3. Glaucoma, defined as IOP over 24 mmHg as measured by applanation tonometry and either confirmed at the next follow-up examination or considered an indication for treatment.

4. Maculopathy, categorized as scarring, macular pucker, cystic macular edema, or radiation retinopathy (retinal hemorrhages, microaneurysms, microinfracts, edema or exudation), evaluated by slit lamp biomicroscopy using a noncontact or contact lens.

5. Optic neuropathy, categorized as radiation papillopathy (edema, peripapillary splinter hemorrhages or microinfarcts) or optic atrophy.

6. Vitreous hemorrhage occurring or recurring after IBT, evaluated by binocular indirect ophthalmoscopy.

7. Retinal detachment (RD) involving at least one quadrant, which first occurred or increased by one quadrant or more after IBT and persisted for more than 6 months, evaluated by indirect ophthalmoscopy or by ultrasonography after visibility to the fundus was compromised. Transient RD that resolved and localized RD directly over or around the tumor was disregarded.

5.4.8. Assessment of Cosmesis (I-II)

Cosmetic outcome was classified as normal, minor abnormality (e.g. persistent redness, inconspicuous scleral thinning, slightly asymmetric pupil, or cataract visible to the naked eye without other cosmetic abnormality) and major abnormality (e.g. visible corneal opacity, rubeosis, or hyphaema, phthisis bulbi, or presence of two or more minor abnormalities). Redness due to recent surgery and similar temporary abnormalities not present at the next examination were not counted.

5.4.9. Retrospective Analysis of Dose Distribution (III)

All 96 treatments of the first study period were retrospectively modeled with a therapy planning software, Bebig Plaque Simulator (BPS; version 4.12, Bebig GmbH, Berlin, Germany) based on prospectively collected data in the registry of the Ocular Oncology Service on the size, shape, and location of the tumor and the axial length (AL) of the eye at

the time of primary treatment. In 50 models, these data and the shape of the eye were obtained from computed tomography and magnetic resonance images. Otherwise, the model was based on clinical and ultrasonographic data in 25 models, and an average AL of 23.0 mm, modified by 0.45 mm for each 1 D of refractive error in 21 models when the AL had not been recorded. For tumors higher than the radius of the eye, the maximum height directly allowed by the BPS, dose to the tumor apex was calculated at the corresponding depth along the tumor central axis.

Each plaque and seed combination was created in the BPS. Templates provided for the Bebig ruthenium plaques and a beta version (5.0.9B3) of the software was used to model two secondary ruthenium treatments for optimal accuracy.[9] The plaques in the model were positioned by consensus of two investigators, based on location of the plaque, transillumination shadow, extraocular muscles, and the limbus as recorded in the patient charts. Typically, the surgeon recorded the distance of the tumor shadow and anterior plaque margin from the limbus and the insertions and margins of adjacent extraocular muscles, and the positions of the fixation holes of the plaque relative to extraocular muscles. In five models, it was necessary to presume that the plaque had slid along the optic nerve, and offset from scleral surface (wobble) was applied accordingly.

In practice, the positioning of the seeds in the plaque may have varied up to 1 mm radially. It was estimated that the position of a round plaque on the scleral surface may have deviated from the modeled position up to 2 mm radially and circumferentially. As a sensitivity analysis, a subgroup of 20 eyes irradiated with the round CCB and CCC plaque (which were used in 80 of the 96 treatments) was drawn at random, and doses to tumor apex and the center of the lens, macula and optic disc were recalculated after a random displacement of either the seeds or the plaque within these limits.

Dose distribution was modeled using linear source approximation, correction for anisotropy, silicon carrier, and gold shell collimation. The following parameters were recorded from the program output: dose and dose rate at tumor base (inner scleral surface) and apex, at the center of the macula and the optic disc, at the posterior pole and center of the lens, at the nearest and farthest point of the chamber angle, and, when applicable, at the retina opposite to the plaque center. Ratios of tumor apex dose to tissue dose, including the previously introduced T:M (tumor apex relative to the macula) and T:D (tumor apex relative to the optic disc) ratios,[11] were calculated.

If a patient had undergone secondary brachytherapy within 3 months of the primary treatment, the doses were added for analysis. If secondary brachytherapy was given later, the patient was censored from analysis at that time.

5.4.10. Extrapolated Response Dose (III)

To take into account the biological effects of dose rate and tissue susceptibility, extrapolated response doses (ERD) for each tissue were calculated from a linear-quadratic equation appropriate for non-permanent implants with a decaying radiation source:[62]

$$ERD = D * (1+[(2R_0\lambda)/(\mu-\lambda)*(\beta/\alpha)]) * [1-\exp(-\lambda T)]^{-1} *$$
$$((1/2\lambda)*[1-\exp(-2\lambda T)] - (\mu+\lambda)^{-1}*[1-\exp(-T(\mu+\lambda))])$$

where D is BPS dose, R_0 is dose rate at the start of treatment, T is treatment time, l is radioactive decay constant (0.693/the half-life of the isotope), a/b is a tissue-specific ratio of two constants representing cell damage and repair, and m is a time constant (0.46 h^{-1}). A small α/β-ratio is typical of healthy, late reacting tissues capable of repairing radiation damage, whereas a large α/β-ratio is typical of early reacting malignant tumors with limited repair capability. An α/β-ratio of 9.75, based on an average α/β of various uveal melanoma cell lines,[300] was used for tumor tissue, 1.2 for the lens,[233] and 2.5 was assumed for retina, optic nerve and other late-reacting normal tissues. Patients who underwent secondary brachytherapy were excluded from the analysis.

5.4.11. Simulation of Treatment with Collimating Plaques (III)

A collimating design for the round CCB and CCC plaques was created with the BPS. Notched COB and CIB plaques were not redesigned because dose to the optic nerve would be high in spite of collimation, and collimation at the limbus would have little effect on already low doses to the fovea and optic disc. Furthermore, the margins of ciliary body tumors are difficult to localize accurately and in both locations scattered radiation outside the plaque margins is likely to improve local tumor control. Patients managed with two sequential plaques or who received secondary brachytherapy were excluded from the analysis.

The CCB and CCC plaques were redesigned to have the same diameter, external shape and number of seeds as the plaques used in the actual treatments, but to be 1.0 mm thicker (Fig.3B). Along the plaque margin, 6 (CCB) or 8 (CCC) seeds were placed in 5.0 mm-long and 1.1 mm-deep slots (offset, 0.6 mm) in the gold shell to obtain a collimating effect

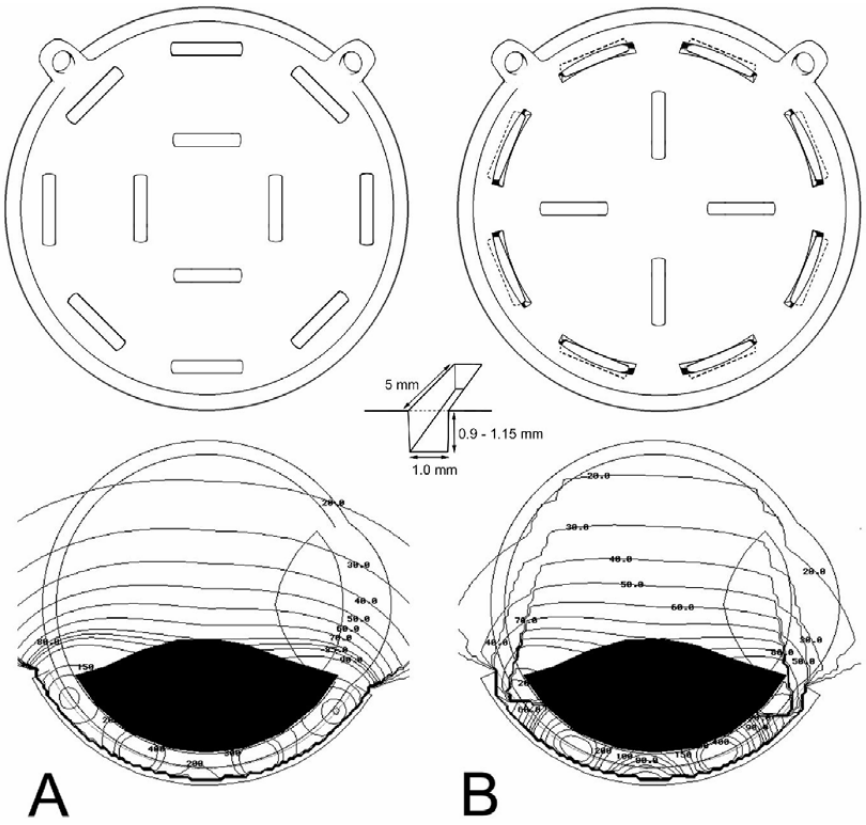

Figure 3. *Diagram showing the concave surface with seed placement and a two-dimensional isodose plot from the plaque simulator software of* ***A*** *the 25-mm CCC plaque used for iodine brachytherapy in our center and* ***B*** *a prototype collimating CCC plaque used in the simulation. Note shift of the isodose curves away from the posterior pole in* ***B****.* ***Inset****, cross-sectional view of a collimating slot.*

that reduces laterally directed radiation. The 4 seeds in the plaque center were not placed in collimating slots in order to ascertain adequate radiation of the entire tumor base. They were, however, arranged as a cross to take advantage of seed anisotropy in reducing radiation to adjacent tissues (Fig.3).

The position of the plaque and the activity of the seeds were taken from the actual IBT. If other than the default number of seeds had been used in the actual treatment (2 with less, 5 with more than the default), the redesigned plaque was loaded with the default number, adjusting the reference date to keep treatment time within two weeks. If the plaque had apparently slid along the optic nerve, the redesigned plaque was moved to avoid the slide.

The end date of treatment was altered, if necessary, to deliver the following prescription dose to the tumor apex: 80 Gy to tumors ≤12 mm or less in height, 70 Gy to tumors >12 and ≤14 mm, and 60 Gy to tumors >14 mm. Dose to the macula and optic disc were calculated with the BPS and compared with corresponding doses from the actual treatment, based on both absolute doses and the T:M and T:D ratios, the latter of which are not influenced by any change in the prescription dose.

5.5. Statistical Methods and Data Analysis

5.5.1. General Guidelines

Follow-up data up to the date of analysis, November 30, 2001 for the studies I-III and May 30, 2004 for Study IV, were prospectively collected into dedicated databases in both study centers.

The data were analyzed with Stata statistical software (Release 7.0, Stata Co., College Station, TX) with the -stcompet- automatic do-file (Boston College Statistical Software Components Archive, available at http://ideas.repec.org/s/boc/bocode.html) and R statistical software (version 1.4.0, The R Foundation for Statistical Computing, Vienna, Austria; available at http://www.r-project.org) with the -cmprsk- library.

Descriptive statistics are given as the median and range and 95% confidence intervals are calculated for key findings. Time-to-event data such as time to development of a complication, local tumor recurrence, and metastatic disease were analyzed by two closely related methods: Kaplan-Meier survival analysis and Cox proportional hazards regression in Studies I and III and cumulative incidence analysis and competing risks regression in Studies II and IV..

5.5.2. The Kaplan-Meier Method

The Kaplan-Meier product limit method is considered the standard in survival analysis. In a setting with no competing risks, Kaplan-Meier provides the most accurate estimates of the proportion of patients with the event of interest. The method, originally developed to assess mortality,[214] assigns each patient in the data set one of two possible outcomes, censored or event. It also assumes that all patients censored from analysis are still at risk of the event of interest.[107] However, when analyzing an event other than death, a patient may be rendered immune to the event of interest by one or more competing risk events and should therefore be removed from the population at risk at that time[107] (e.g. an eye cannot develop a cataract after enucleation nor can a patient become blind after dying of metastatic melanoma). Using the Kaplan-Meier method in a setting with frequent competing risks tends to overestimate the proportion with the event analyzed. On the other hand, it also excludes the effect of competing events from the analysis where they can be considered confounding factors as regards the aims of the study.[41;43] If the effect of competing risks is relevant for the aim of the study, it is preferable to use cumulative incidence analysis instead.

5.5.3. Cumulative Incidence Analysis

Cumulative incidence analysis takes competing risks into account by considering a third possible outcome in addition to censored and event: a competing risk event. A patient with a competing risk event is censored from the analysis but not considered to be at risk of the event of interest like those censored at the end of follow-up. This avoids overestimating the remaining population at risk, and consequently, the incidence of the outcome.

For example, in the analysis of ocular complications (II), death and enucleation were modeled as competing events, after the occurrence of which the patient was no longer at risk of the event of interest.

5.5.4. Analysis of Survival (I)

Analyses of both all-cause and melanoma-related survival were based on the Kaplan-Meier method.[137] To address selection bias, the survival of all 121 patients who had large uveal melanomas was also assessed.

5.5.5. Analysis of Local Tumor Recurrence, Eye Retention, Metastases and Cosmesis (I)

In the first study, Kaplan-Meier analysis was used to assess time to secondary enucleation and time to development of local recurrence, metastases, and abnormal cosmetic appearance of the tumor eye. In Study II, the same outcomes were assessed with cumulative incidence analysis for comparison when this method became available. In Study IV, cumulative incidence analysis was used to assess local tumor recurrence.

5.5.6. Analysis of Vision Loss (I-IV)

This key outcome was analyzed using several different approaches. The main endpoints were development of unilateral low vision (VA 20/70 or worse) and unilateral blindness in the study eye (VA less than 20/400) using the World Health Organization criteria (I,III,IV). In Study I, these were assessed using the Kaplan-Meier method and in Studies III and IV with cumulative incidence analysis.

In order to facilitate comparison with the COMS studies two additional approaches were used. First, mean VA, after transformation to a logarithmic scale and stratified by factors associated with poor vision outcomes, was plotted at 6-month intervals (I,IV).[189] Measurements below 20/1600, such as counting fingers or hand movement, were set equal to 20/1600. Enucleated eyes and eyes with no light perception were counted as having 20/2500 vision.[189] If the patient did not have a measurement available at all appropriate intervals, the

VA was taken to be the average of the previous and the next visits.[189] If there was a longer gap in follow-up, the patient was censored from the analysis. The second approach analyzed time to loss of VA 20/40, 20/70 and 20/200, and loss of more than six lines of vision, corresponding to quadrupling of the minimal angle of resolution from the baseline, using the Kaplan-Meier method in accordance with the COMS Medium Tumor Study. Loss of vision was recorded only when confirmed at the next follow-up examination.[189]

Person-years of vision conserved in the study eye was estimated by counting the total time at risk for the COMS and WHO adverse visual outcomes, allowing for recovery and repeated loss of vision with the multiple-failures per subject analysis (I). In Study IV cumulative frequency of VA levels at baseline and at 1, 2, and 3 years after diagnosis was also plotted, and compared using the Kruskal-Wallis test.

5.5.7. Analysis of Complications (II-IV)

Cumulative incidence instead of Kaplan-Meier analysis was chosen to analyze time to individual complications in Studies II and IV, because the aim was to provide realistic estimates of incidence for clinicians for counseling and deciding on appropriate therapy for patients with a large uveal melanoma, a setting with frequent competing risks, particularly metastatic death.

Kaplan-Meier analysis, which censors patients from the analysis when competing risk events take place, provides unbiased estimates of the probability of complications in patients who do not encounter any competing risk events.[43] Because the aim of Study III was to analyze late complications in order to reduce them, if possible, in surviving patients treated in the future, and to isolate the effect of dose-related variables, the Kaplan-Meier method was chosen to factor out the effect of competing risks. Kaplan-Meier survival curves were used to summarize time to complications of interest for descriptive purposes in Study III. To visually assess threshold doses and dose ratios, the curves were superimposed with a scatterplot depicting the dose received by an individual patient and the reason for censoring the patient from analysis, if applicable.

To assess the prevalence of potentially reversible complications (cataract, abnormal IOP, vitreous hemorrhage, and RD), the proportion of patients with the complication was calculated at each time point. Patients with missing data were considered to have a complication if it was present at the previous and a subsequent visit no more than 6 months later. A patient with longer data gaps and those with a missing IOP measurement were censored from the calculation at that time point.

5.5.8. Number Needed to Treat (I,IV)

The number of patients needed to treat with IBT instead of enucleation for one additional patient to benefit (NNTB) by maintaining 20/400 vision or better in the tumor eye for at least 2 years from treatment was calculated with its 95% confidence interval using the Wilson score method.[5;30]

The number of patients needed to treat with TSR instead of IBT to achieve the same benefit was assessed in Study IV. This method was also used to estimate the harm from local tumor recurrence were the patients managed with TSR instead of IBT. A negative number needed to treat indicates that one additional patient will be harmed (NNTH) by the treatment for the specified number of patients treated.

5.5.9. Proportional Hazards Regression

Proportional hazards regression models were used to assess individual baseline tumor and host-related risk factors associated with time to vision loss and time to each complication after treatment. In Studies I and III employing the Kaplan-Meier method, Cox proportional hazards regression models were used. Cumulative incidence analysis with competing risks regression (CRR) models were used to assess complications in Studies II and IV. Factors predicting vision loss were modeled in Studies I and III with Cox proportional hazards regression, based on both single-failure (time to first event) and multiple-failure (repeated events) data sets.[56;297] Because competing risks regression, as currently implemented in available software, can not be used to appropriately analyze counting process type data, multiple-failure models for vision loss could not be used in Study IV.

In Studies I and II associations between individual risk factors and events of interest were first studied at univariate level. Age at diagnosis, LBD, tumor height and the distance of posterior tumor margin to FAZ were modeled as continuous variables. Location of the anterior tumor margin was dichotomized (behind the ora serrata, in the ciliary body). Variables were selected to multivariate models from those explanatory variables that were significantly associated ($P<0.10$) with the event of interest by univariate analysis, and from generally known potential confounders (e.g. increasing age predisposes to cataract). Confounding variables were kept in the model irrespective of statistical significance.[124] In Study III, dose-related variables that were significant at univariate level were entered into models based on previous studies to assess whether they better explain the recorded events. In Study IV, the effect of treatment type (TSR vs. IBT) on complications was assessed using competing risks regression models based on best-fitting models from Study II.

The number of variables in the final model was restricted, based on a rule to have at least 15 to 20 events per each additional variable.[214] The assumption of proportional hazards was tested by the method of Therneau and Grambsch,[297] which utilizes scaled adjustment of Schoenfeld residuals, allowing interpretation of the smoothed residuals as a nonparametric estimate of the log hazard ratio function, both globally and for individual covariates in the model. The regression coefficients and hazard ratios (HR) with 95% confidence intervals were calculated. Standard errors were calculated using the robust variance estimator of Lin and Wei,[170] and tied survival times were handled with Efron approximation.[137] Models were compared using the deviance test.[137]

5.5.10. Logistic Regression (IV)

In Study IV, an exploratory Cox proportional hazards regression model for VA loss did not fulfill the assumption of proportional hazards.[297] Instead, logistic regression models which included treatment type and patient age, tumor height-to-diameter (H:D) ratio and baseline VA as confounders, were used to analyze VA loss at 1, 2, and 3 years from treatment.

5.5.11. Analysis of Agreement and Uncertainty in Dose Calculation (III)

Agreement in dose calculation between the original treatment planning and BPS was assessed by plotting the difference between the measurements against their mean, and by calculating the mean difference.[4] Uncertainty in the BPS doses to adjacent tissues, based on the sensitivity analysis, was estimated with the same method.

6. Results and Discussion

6.1. Iodine Brachytherapy for Large Uveal Melanomas – Results, Complications and the Effect of Dose Distribution (I-III)

6.1.1. Baseline Population Characteristics

The median age at diagnosis of the 97 patients (male:female, 49:48), all Caucasian, managed with IBT was 64 years (range, 24-82). The median follow-up time was 3.5 years (range, 0.3-10.4). Only three patients had 20/20 vision at diagnosis, whereas 29 (30%) had an acuity of 20/200 or worse (Table 1 in I). According to the WHO definitions, 35 (36%) study eyes had low vision and 19 (19%) were blind.

6.1.2. Baseline Tumor Characteristics

The median tumor height and LBD were 10.7 mm (range, 4.5-16.8) and 16.1 mm (range, 7.3-25.0), respectively (Fig.4A). Of the 97 tumors, 10 (10%) were classified large based on their peripapillary location,[57] and 61 (63%) involved the ciliary body. The posterior margin of the tumor touched the optic disc in 15 (15%) eyes and extended to within 2 mm of it in 8 (8%) eyes (Fig.4C). The median distance to the center of the foveal avascular zone (FAZ) was 6.0 mm (range, 0-18).

As compared to the COMS Large Tumor Study (Table 1 in I)[57], the tumor height was skewed toward higher values (mean, 10.8 vs. 9.5 mm; $P < 0.001$ Kruskal-Wallis test), and the LBD toward smaller values (mean, 16.2 vs. 17.2 mm; $P = 0.001$ Kruskal-Wallis test).

6.1.3. Dose Distribution and Dose Rate

The tumor apex (prescription point) was a median of 11.3 mm from the outer scleral surface. The median prescribed dose was 87 Gy (range, 42-109) at a median dose rate of 57 cGy/h (range, 13-217, Fig.5A). Median treatment duration was 147 hours (range, 42-599).

The median BPS dose at tumor apex and tumor base was 81 Gy and 384 Gy (Fig.6). The median dose rates at these points were 53 cGy/h (range, 11-204) and 289 cGy/h (range, 84-1213), respectively. The range of dose rates at tumor apex was considerably wider than the ones stated in the COMS protocol and the American Brachytherapy Society (ABS) recommendations (Fig.5A). The median BPS doses to the center of the macula and optic disc were 79 Gy and 83 Gy (Fig.6). The median T:M ratio was 1.03 (range, 0.12-6.65), and the median T:D ratio was 0.97 (range, 0.27-8.21).

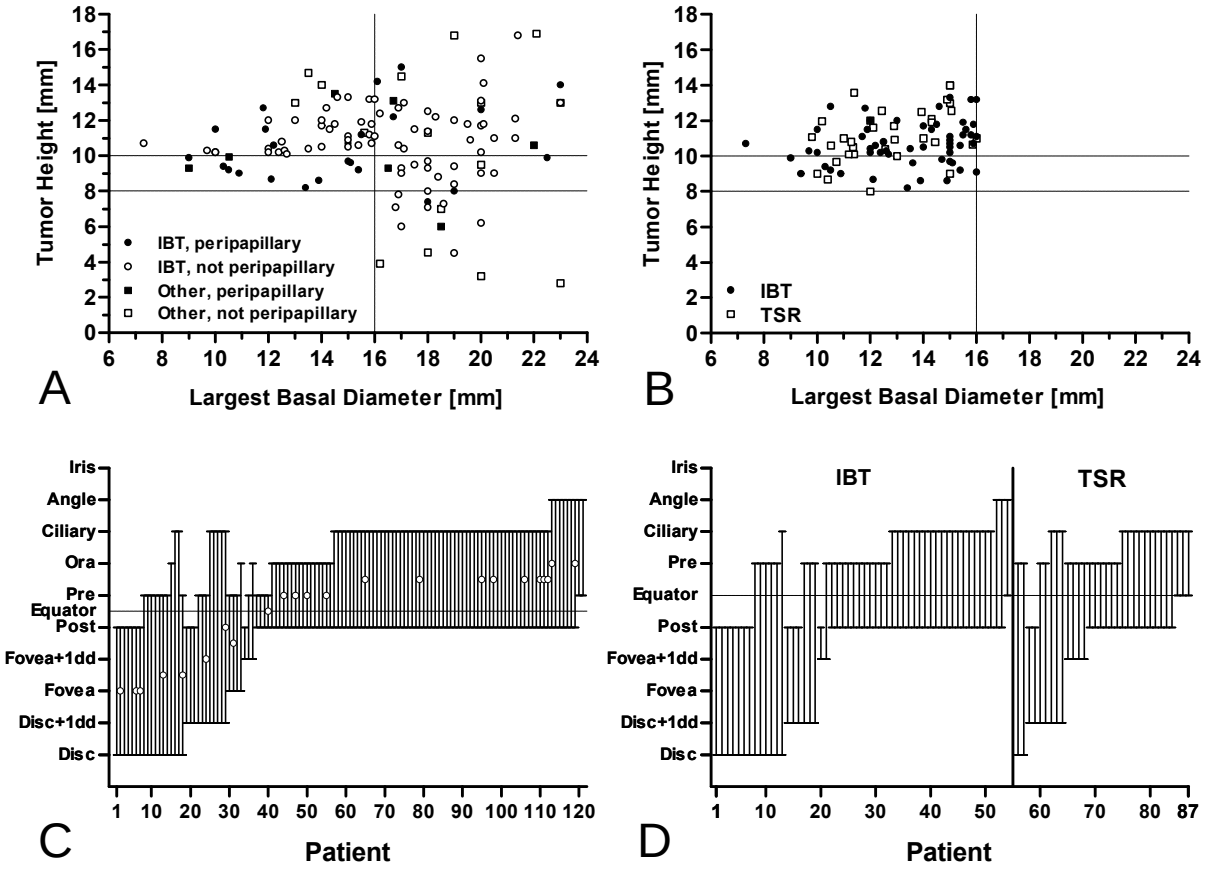

Figure 4. *Size and location of the uveal melanomas in the present study.* ***A,*** *Scatter plot of largest tumor basal diameter against tumor height of the 121 large tumors of which 96 were managed with primary iodine brachytherapy (IBT). Circles indicate tumors managed with IBT. Tumors closer than 2 mm from the optic disc were considered peripapillary. The dashed lines indicate the COMS criteria for a large tumor.* ***B,*** *Similar plot of the 87 tumors that were large because of tumor height and were managed by either IBT or transcleral local resection (TSR) and enrolled in the fourth part of the study.* ***C and D,*** *Plot of tumor location in studies I-III and IV, respectively. Bars indicate the position of the anterior and posterior margin of each tumor.*

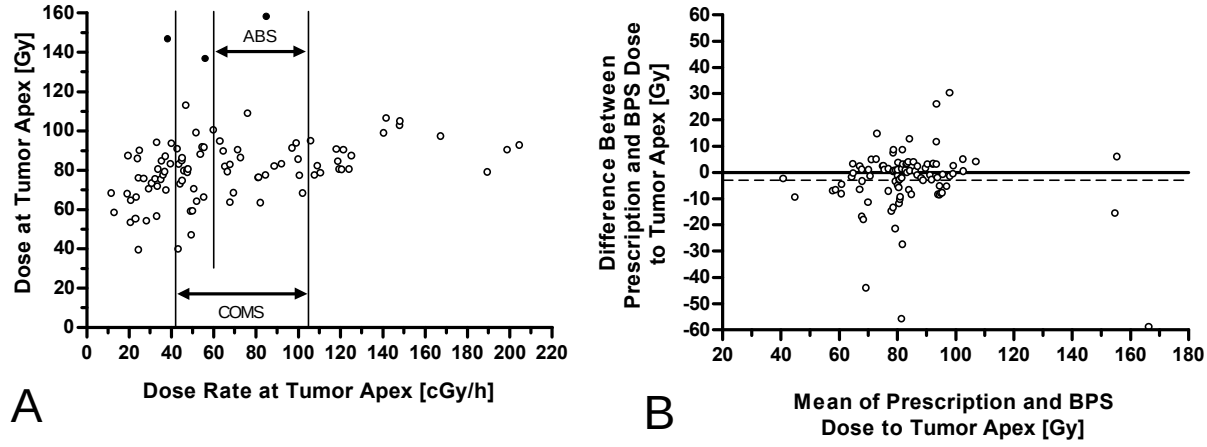

Figure 5. *Scatterplot of dose to tumor apex against corresponding dose rate for 96 patients with a large uveal melanoma who underwent iodine brachytherapy (**A**).* Vertical bars *show Collaborate Ocular Melanoma Study (COMS) and American Brachytherapy Society (ABS) guidelines for dose rate, and* solid dots *indicate primary treatment with two sequential plaques. (**B**) Scatterplot of agreement between originally calculated dose to tumor apex and corresponding dose calculated with the plaque simulator software (BPS).* Dashed line *indicates mean difference between doses.*

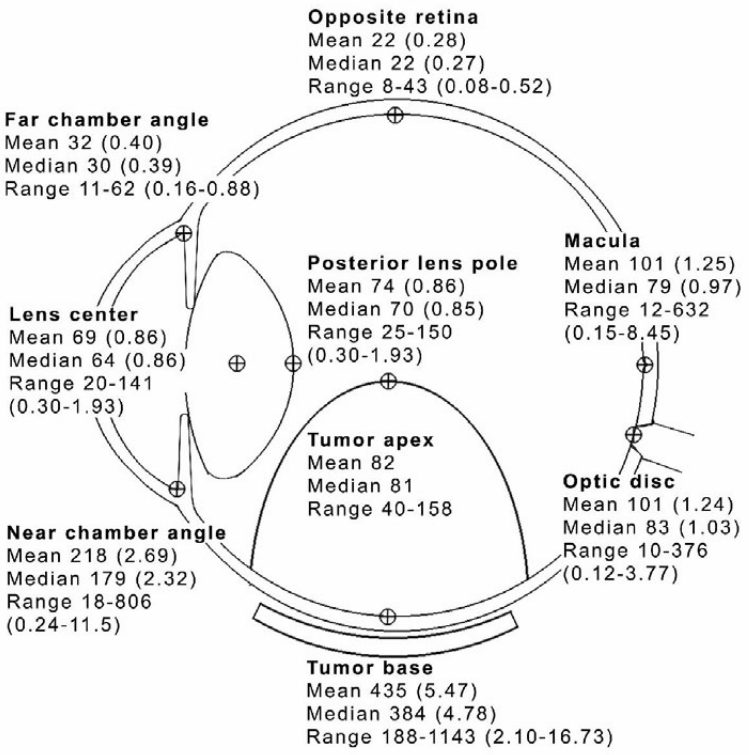

Figure 6. *Diagram showing mean dose, median dose and dose range in Grays to specific points of the tumor and the eye as calculated with the plaque simulator software for 96 patients with large uveal melanomas who underwent iodine brachytherapy. Numbers in parentheses indicate the mean, median and range of the ratios of the corresponding dose relative to the dose at tumor apex.*

The mean difference between the prescription and BPS dose at tumor apex was -2.8 Gy (range, 59 Gy decrease to 30 Gy increase, Fig.5B). In 78 (81%) eyes, the BPS dose was within ±10 Gy of the prescribed dose. Differences greater than 10 Gy were most likely the result of probable sliding of the plaque along the optic nerve (5 eyes), misjudgment of tumor height because of oblique B-scans in some early treatments (8 eyes), and overestimation of total dose to tumor apex from two partly overlapping subsequently applied plaques (2 eyes).

Sensitivity analysis indicated mean differences in BPS dose to the macula and the optic disc due to random error in plaque positioning were -5 Gy and -4 Gy (Fig.2C in III), respectively, and mean differences due to random seed displacement were -2 Gy and +0.4 Gy (Fig.2D in III), respectively. Differences of more than ±20 Gy in BPS dose to the macula and optic disc were rare, but occurred when the plaque was within 1 mm of these structures and the BPS dose was consequently high (Fig.2C,D in III).

The accuracy of the Bebig Plaque Simulator has been evaluated by others,[162;209] and it has proven to be a reliable tool for brachytherapy planning. In most of the retrospective cases modeled in the present study, the simulated dose matched the prescribed dose very closely and, given the three-dimensional detail of the BPS treatment plan, the former is likely to be a closer estimate of the dose actually delivered. This is especially true in cases where the simulation showed that, provided that the AL and/or MRI measurements of the eye size and the location of the sutures documented in the surgery report were accurate, the plaque must

have tilted along the optic nerve sheath during placement. With therapy planning software such as the BPS, which considers the individual anatomy of the tumor eye, such difficulties can be predicted in the planning phase and miscalculations of the dose distribution limited.

6.1.4. Survival

Of the 97 patients, 34 died during the follow-up and 28 of these deaths were classified as being due to metastatic uveal melanoma. Of the 28 melanoma deaths, 19 (68%) were histopathologically confirmed (17 were diagnostic of and two consistent with metastatic melanoma), and nine were suspected on the basis of clinical data. Additional eight patients were alive a median of 14 months (range, 2-32) after diagnosis of metastases. One patient was dead of histopathologically confirmed metastatic carcinoma of the colon and five patients died without evidence of melanoma metastases (three of myocardial infarction and two of cerebrovascular accident).

The Kaplan-Meier estimate for all-cause survival was 62% at 5 years (95% CI, 49-72%) and 48% at 8 years (95% CI 33-61%; Fig.7A) The estimated melanoma-specific survival was 65% (95% CI, 52-75%) and 54% (95% CI, 38-68%) at 5 and 8 years respectively (Fig.7B). These survival curves are visually comparable to the melanoma-specific survival after enucleation in the COMS Large Tumor Study (based on the originally published graph,[294] which corresponded to melanoma-specific mortality defined as death with histopathologically confirmed metastasis or, if histopathology was not available to confirm

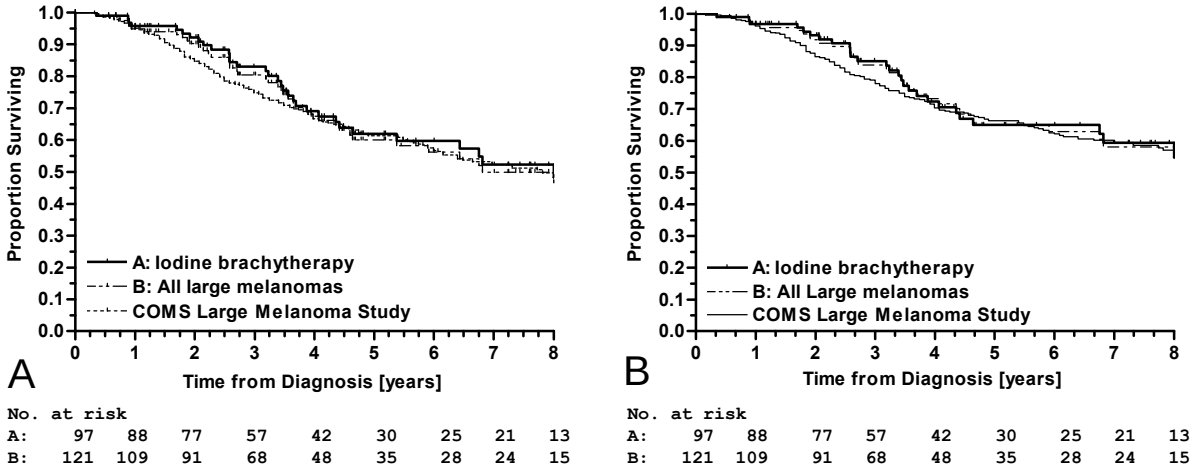

Figure 7. ***A,*** *Kaplan-Meier plot of all-cause survival for 97 patients with uveal melanoma large by Collaborative Ocular Melanoma Study (COMS) criteria who were managed with iodine brachytherapy (IBT). Survival for the entire series of 121 patients with large uveal melanomas, and for patients who underwent enucleation without prior irradiation in the COMS Large Tumor Study are shown for comparison.* ***B,*** *Corresponding plot of melanoma-specific survival, based on histopathologically confirmed or suspected melanoma metastasis.*

the source of metastasis, with suspected melanoma metastasis; Diener-West M, personal communication, 2002). This is in spite of the fact that, unlike COMS, the present study did not exclude patients who had a history of major illness, other cancer or metastases at diagnosis. Using cumulative incidence to allow for competing causes of death, melanoma-specific survival was 66% (95% CI, 55-77%) at 5 years and 57% (95% CI, 44-71%) at 8 years.

The results are also in line with those from other studies of predominantly large uveal melanomas.[237;246] In can be argued, however, that the median follow-up of 3.5 years of the present study was insufficient to reveal a possible late increase in mortality caused by post-treatment metastasis spawned by viable tumor cells. Based on tumor doubling times it has been estimated that a follow-up less than 8 years may not detect this late increase in mortality.[180] However, no such late increase in mortality has been noted in any studies on eye-conserving management of uveal melanoma with longer follow-up.[20;24;51;108] This issue should nevertheless be revisited when long-term follow-up data after IBT becomes available.

6.1.5. Tumor Regression and Local Tumor Recurrence

After IBT, tumor height regressed a median of 38% (range, 85% [14.3 mm] decrease to 5% [0.5 mm] increase) by 1 year and 48% (range, 82% [10.7 mm] decrease to 4% [0.4 mm] increase) by 3 years. By 1 and 3 years, 30% and 23% of tumors had regressed by less than one third, and 14% and 23% had regressed by two thirds or more in height, respectively.

Local tumor recurrence was diagnosed in 5 patients, all within 3 years from treatment. Two were classified as extrascleral marginal (perilimbal at tumor margin), two as vertical and one as a ring melanoma. Two were controlled with additional IBT (one later developed an extrascleral marginal recurrence) and three were managed with secondary enucleation. The Kaplan-Meier estimate for developing first local recurrence was 6% (95% CI, 2-14%) by 5 years (I). The 5-year cumulative incidence of local tumor recurrence was also 6% (95% CI, 2-12%; Fig.8A), lower than those of the competing risks, secondary enucleation (11%) and death (44%). The small number of locally recurring tumors in this data set precluded a regression analysis of baseline risk factors for recurrence.

The 5-year 6% recurrence rate compares favorably with the 10.3% risk of treatment failure at 5 years[143] reported by the COMS Medium Tumor Study and with several observational series with mainly medium-sized tumors, in which the 5-year Kaplan-Meier estimate for developing local tumor recurrence after IBT has ranged from 8% to 20%.[219;220;267] This is irrespective of the fact that, if indicated to reduce radiation to the optic disc and

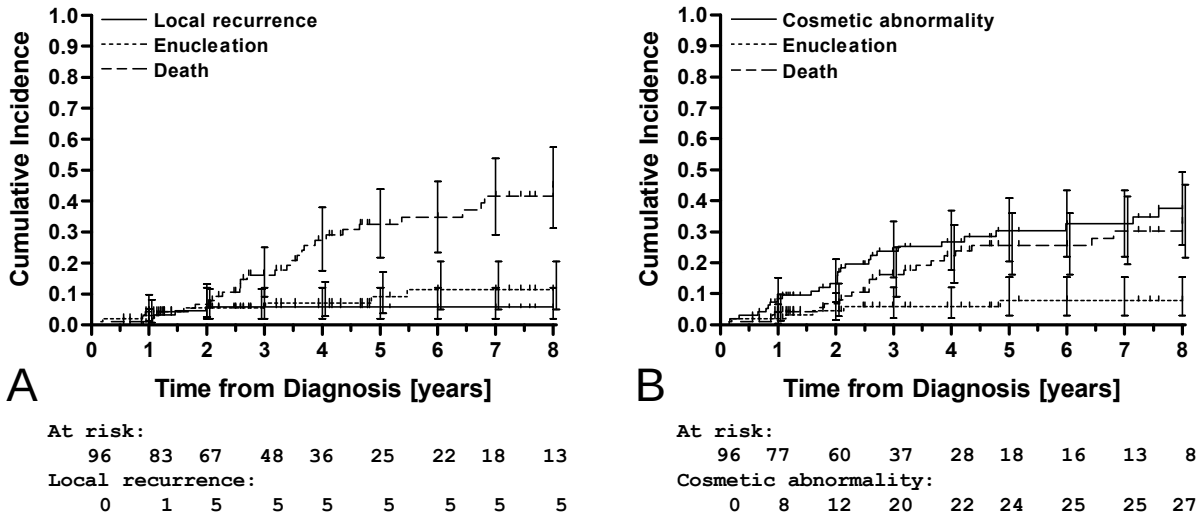

Figure 8. *Cumulative incidence of **A**, local tumor recurrence; **B**, cosmetic abnormality of the tumor eye after iodine brachytherapy of a large uveal melanoma. Cumulative incidence of secondary enucleation and death, the main competing risks, are also plotted. Bars indicate 95% confidence intervals and ticks show censored observations.*

macula or to cover a very large tumor, an absolute 2 mm safety margin around the tumor was not required in the present study. The plaques used differed from the COMS plaques in that they do not have a collimating rim, and coverage of the tumor with a smaller safety margin was considered sufficient because of lateral scatter of radiation.[11] A prescription dose lower than the 85 Gy required by COMS was used to treat very thick tumors, and the dose rate was allowed to vary more widely.[76]

The possibility that some recurrences may have been missed must be considered, because in several eyes treatment-related complications eventually prevented view to the fundus. Secondary enucleation was offered when visibility was lost, but most patients declined further therapy in the absence of evidence of recurrence unless the eye was irritated and enucleation promised symptomatic relief. So far, no delayed recurrences have been observed, although these patients are closely reviewed both by standard and high-frequency ultrasonography and by periodic CT and MRI, and the longest follow-up times exceed 13 years. Furthermore, considering that the risk of dying of metastatic melanoma by cumulative incidence analysis was more than seven times higher that that of recurrence at 5 years, it is also possible that some large tumors, which would have recurred locally after IBT, caused metastatic death before a local recurrence was observed.

The data suggest that large tumor size does not predict more frequent local recurrence after IBT as compared to medium-sized tumors.[219;220;267] This conclusion, also, should be revisited when follow-up data accumulates. Local recurrence has been associated with high risk of metastasis,[81;128;305] but it is not known whether this is because tumor cells

disseminate from the recurring tumor or because of greater inherent malignancy of tumors that recur.[53] Finding the answer merits further research, since it would not only greatly influence the treatment conventions but also increase our understanding of the metastatic process.

6.1.6. Eye Retention and Cosmetic Outcome

In addition to the three eyes removed after recurrences, one primary enucleation instead of IBT was performed when extraocular extension was detected at surgery, and eight eyes were removed a median of 12.5 months (range, 0.3-58) after diagnosis because of complications, mostly uncontrollable neovascular glaucoma. The Kaplan-Meier estimate for conservation of the eye was 84% (95% CI, 72-92%) at 5 years (Fig.2E in I).

It is important to note, that eye retention rate as a measure of success of the primary treatment is confounded by the indications for secondary enucleation of the study center, which makes direct comparison between reports misleading. The present study represents a rather conservative approach to enucleation. This is a result of both the clinical conventions of the study center and the reluctance of many patients to undergo enucleation, sometimes even when usable visual acuity and fundus visibility were lost and enucleation was recommended as a safety measure.

Of the retained eyes, 41 had normal cosmesis at last follow-up. The 5-year cumulative incidence of any cosmetic abnormality was 30% (95% CI, 20-41%; Fig.8B). The risk of developing complications which result in symptoms and discomfort in the tumor eye is probably one major reason why enucleation has been recommended as primary therapy for large uveal melanoma. This used to be the practice at this study center, too, but experience has proven that, given the option, most of our patients elect IBT in spite of these unfavorable odds. Ocular oncologists in general pay more and more attention to the patient's own objectives when discussing treatment.[64;68]

6.1.7. Preservation of Visual Acuity

Among the 96 patients, five avoided low vision for at least 2 years. The cumulative incidence of low vision was 76% (95% CI 61-85%) at 1 year, 85% (95% CI, 71-93%) at 2 years, and 93% (95% CI, 80-98%) at 3 years (Fig.9A).

Sixteen patients avoided blindness for at least 2 years. The cumulative incidence of blindness was 47% (95% CI, 35-57%) at 1 year, 69% (95% CI, 57-78%) at 2 years, and 84% (95% CI, 73-91%) at 5 years (Fig.9B).

A total of 49 person-years without low vision (median, 0.6 years per patient who initially had this level; range, 0.04-8.2) and 111 person-years without blindness (median, 1.0 year; range, 0.03-8.6) of the study eyes were saved by IBT compared to enucleation.

6.1.7.1. Clinical Factors Predicting Visual Loss

By univariate, single-failure Cox regression analysis, tumor height was a significant risk factor for developing low vision and blindness in the study eye (hazard ratio [HR] 1.38 and 1.31 for each mm increase, P = 0.001). Age at diagnosis was also a significant risk factor for low vision (I). By multiple-failure analysis, which allows repeated loss and recovery of vision (I), location of the anterior tumor margin behind the ora serrata became a significant predictor of blindness (HR 1.68, P = 0.011) and distance of the posterior tumor margin from FAZ a predictor of both low vision and blindness (HR 0.94 for each mm increase, P = 0.009 and 0.010, respectively) in the study eye. LBD was not significantly associated with visual loss in any analysis.

Bivariate regression identified tumor height on one hand, and location of the anterior tumor margin behind the ora serrata and short distance from posterior tumor margin to the FAZ on the other hand, as independent predictors of both low vision and blindness in the study eye. The model which combined height with location of the anterior tumor margin better predicted development of low vision in the study eye by single-failure analysis than the alternative model, which included distance to FAZ, and the two models were comparable by

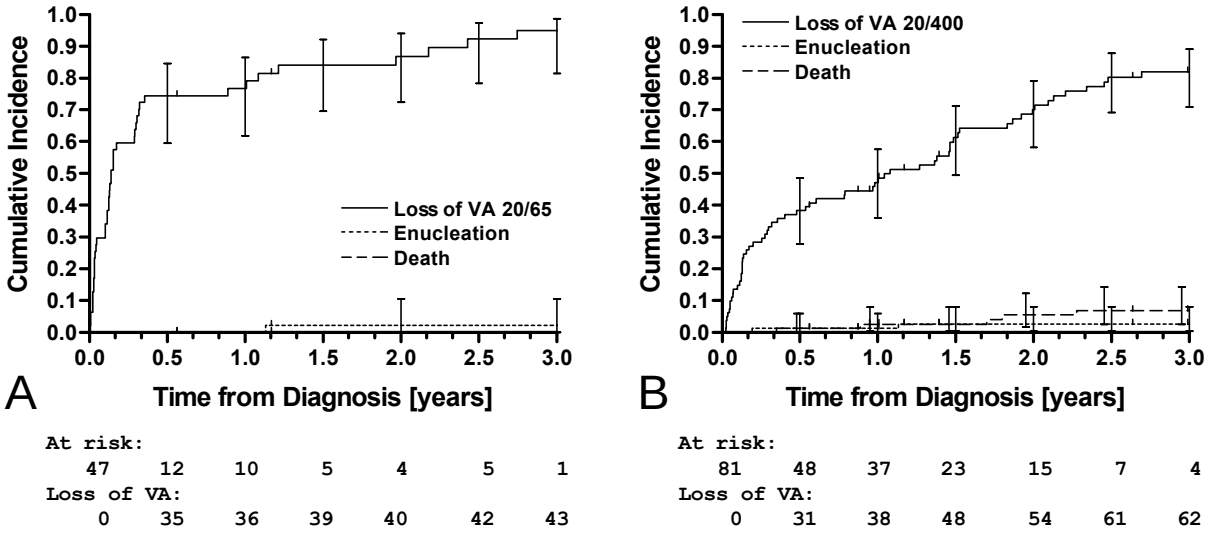

Figure 9. *Cumulative incidence of **A**, first loss of 20/70 and **B**, first loss of 20/400 visual acuity (VA) level, corresponding to the World Health Organization's definitions of low vision and blindness, respectively, after iodine brachytherapy of a large uveal melanoma. Cumulative incidence of secondary enucleation and death, the main competing risks, are also plotted. Bars indicate 95% confidence intervals and ticks show censored observations.*

Table 3. *Cox proportional hazards regression of time to low vision (20/70 or worse) and blindness (loss of 20/400) in the study eye, based on single and multiple failure data sets*

	Single failure				***Repeated failure***			
Variable	**Coefficient (SE)**	**Wald chi-square**	**P**	**Hazard ratio (95% CI)**	**Coefficient (SE)**	**Wald chi-square**	**P**	**Hazard ratio (95% CI)**
BIVARIATE ANALYSIS								
Low Vision	-2 Log Likelihood = 214.05					-2 Log Likelihood = 351.18		
Tumor height†	0.427 (0.101)	17.8	<0.001	1.53 (1.26-1.87)	0.310 (0.066)	22.0	<0.001	1.36 (1.20-1.55)
Anterior tumor margin‡	1.237 (0.408)	9.18	0.002	3.45 (1.55-7.67)	0.672 (0.206)	10.0	0.001	1.96 (1.31-2.93)
Blindness	-2 Log Likelihood = 418.67					-2 Log Likelihood = 614.12		
Tumor height†	0.333 (0.089)	14.1	<0.001	1.39 (1.17-1.66)	0.266 (0.065)	16.6	<0.001	1.30 (1.15-1.48)
Anterior tumor margin‡	0.689 (0.285)	5.86	0.016	1.99 (1.14-3.48)	0.796 (0.210)	14.3	<0.001	2.22 (1.47-3.35)
TRIVARIATE ANALYSIS								
Blindness	-2 Log Likelihood = 410.62					-2 Log Likelihood = 604.86		
Tumor height†	0.338 (0.091)	13.9	<0.001	1.40 (1.17-1.68)	0.253 (0.062)	16.6	<0.001	1.29 (1.14-1.45)
Anterior tumor margin‡	0.763 (0.337)	5.11	0.024	2.14 (1.11-4.15)	0.670 (0.243)	7.62	0.006	1.95 (1.21-3.14)
Distance to FAZ†	0.014 (0.034)	0.17	0.68	1.01 (0.95-1.08)	-0.027 (0.027)	1.04	0.31	0.97 (0.92-1.03)

SE = Standard error, CI = Confidence interval, FAZ = Foveal avascular zone

†Continuous variable, mm ‡Categories: 0 = in the ciliary body, 1 = behind the ora serrata

multiple-failure analysis. They were also comparable in predicting development of blindness, but in a trivariate model location of the anterior tumor margin became the predominant predictor of blindness as well, together with tumor height (Table 3).

Although the long-term prognosis of preserving vision in an irradiated eye is poor for most patients with a large uveal melanoma, even short-term conservation of vision in the tumor eye appears to be preferable to many patients as compared to immediate blindness from enucleation. Furthermore, because some patients maintain usable vision after IBT of a large uveal melanoma, identifying the risk factors for VA loss can help in refining the treatment protocol in order to extend this benefit to more patients.

6.1.7.2. Association Between Dose and Vision Loss

By univariate Cox regression, low vision and blindness of the tumor eye were associated with dose to the optic disc (HR 1.04 and 1.06 for each 10 Gy increase, P=0.035 and P=0.001, respectively, Table 2 in III) and macula (HR 1.06 and 1.10 for each 10 Gy increase, P=0.025 and P<0.001, respectively). In bivariate models with tumor height, dose to the macula independently predicted low vision and blindness whereas dose to the optic disc independently predicted only blindness (Table 2 in III).

Dose to the macula lost association with low vision in a trivariate model with tumor height and location of the anterior tumor margin in the ciliary body (Table 2 in III), another factor associated with vision loss in this data set. This model did not provide a better fit than the corresponding bivariate model without ciliary body involvement. Dose to the macula remained associated with blindness in a similar trivariate model, but this model did not improve fit (P=0.10). Tumor height retained an independent association with loss of vision in all models. Dose to the optic disc showed a weaker association with low vision than dose to the macula, and provided a poorer fit as regards blindness (Table 2 in III).

The fact that loss of visual acuity was strongly related to the dose to the macula and optic disc suggests that visual prognosis for these patients could be improved through a more favorable dose distribution. However, tumor height, which correlates to the dose to adjacent tissues and to tumor volume, remained independently associated with loss of vision even when adjusted for dose to the macula and optic disc. This is an interesting finding, since tumor height can also act as a surrogate variable for dose to key ocular tissues in brachytherapy. This finding may reflect other adverse effects caused by the presence of a large tumor, which are independent of radiation. It also indicates that, for clinical purposes,

tumor height remains a robust predictor of high risk of major complications and vision loss after IBT of a large choroidal and ciliary body melanoma.

6.1.7.3. Number Needed to Treat

The Number Needed to Treat (NNT) was 14 patients to allow one patient to retain 20/70 vision or better in the treated eye for at least 2 years, and the NNT was 6 to avoid blindness of the treated eye in one patient for at least 2 years. It is impossible to predict which patients will enjoy such a benefit after IBT, but both stratification by potential prognostic factors and Cox multiple regression analysis suggested that location of the anterior tumor margin in the ciliary body in addition to decreasing tumor height was the factor most consistently associated with smaller risk of both low vision and blindness in the treated eye. Furthermore, because uveal melanomas with ciliary body involvement are also associated with shorter survival,[168] the benefit from enucleation as regards avoiding potential treatment-related complications is smallest for these patients who are at a greater risk of developing metastases early and dying soon after diagnosis.

6.1.8. Complications and Their Management

6.1.8.1. Kaplan-Meier vs. Cumulative Incidence in Reporting Complications

Ocular complications were frequent after IBT of a large uveal melanoma. Expectedly, death of metastatic melanoma was an important confounder. The cumulative incidence estimates of various complications developing were a median of 6 percentage points lower than estimates based on standard Kaplan-Meier analysis (Table 4). It seems reasonable to use cumulative incidence analysis for reporting results of conservative treatment of eye cancer to avoid exaggerating the frequency of the side effects. Until an effective treatment for disseminated disease is found, a substantial number of patients with a large melanoma will succumb before complications from treatment develop. Because of this, Kaplan-Meier analysis will provide patients with an overly pessimistic estimate to consider when deciding whether or not to choose IBT instead of enucleation.

6.1.8.2. Cataract

Cataract progressed in 65 patients, including those who received the lowest doses to the lens (Fig.10A). By cumulative incidence analysis, cataract developed or progressed in 79% (95% CI, 68%-86%) of the 89 phakic eyes within 5 years of IBT.

Table 4. *Comparison between cumulative incidence and Kaplan-Meier estimates of the 5-year incidence of complications after iodine-125 brachytherapy of 96 patients with a uveal melanoma large by the Collaborative Ocular Melanoma Study criteria*

Complication	Proportion with Event		
	Cumulative Incidence Estimate	Kaplan-Meier Estimate	Difference‡
Cataract	79 %	85 %	6 (8 %)
Iris neovascularization	62 %	68 %	6 (10 %)
Glaucoma	60 %	66 %	6 (10 %)
Maculopathy	52 %	59 %	7 (13 %)
Optic neuropathy	46 %	53 %	7 (15 %)
Vitreous hemorrhage	36 %	39 %	3 (8 %)
Retinal detachment	25 %	27 %	2 (8 %)
Recurrence	6 %	6 %	<1 (9 %)
Cosmetic abnormality	30 %	37 %	7 (21 %)
Loss of 20/60 acuity	95 %	97 %	2 (2 %)
Loss of 20/200 acuity	85 %	94 %	9 (11 %)

‡ percentage points (% higher than the cumulative incidence estimate)

By competing risks regression, tumor height (*P*=0.017) was associated with time to cataract progression. In a trivariate model (Table 5), which took into account age and diabetes (HR 1.78) as confounders, tumor height increased in significance. In a univariate Cox regression model which included simulated dose, time to cataract progression was associated with dose to the center (HR 1.15 for each 10 Gy increase, P=0.002) and posterior pole (HR 1.14 for each 10 Gy increase, P=0.003) of the lens. A trivariate model, which combined dose to the lens center with age at diagnosis and diabetes as confounders (Table 6) did not improve fit over the model based on the same confounders and tumor height (-2 Log likelihood 472.83 vs. 472.40, P=0.56, chi-square test, 1 df).

Of the 65 patients whose cataract progressed after IBT, 27 (42%) underwent cataract surgery without complications, and 25 of these received an intraocular lens. Five years after treatment, 43% (95% CI, 25-63%) of survivors had clinically significant lens opacity in the treated eye and 57% (95% CI, 37-75%) had undergone cataract extraction either before or after IBT (Fig.2A in II).

It seems, that with a large uveal melanoma it is difficult to avoid secondary cataract. Fortunately, reports suggest that cataract extraction from an eye with a treated uveal melanoma is a safe procedure,[110;220;306] which was also the case in the present data set.

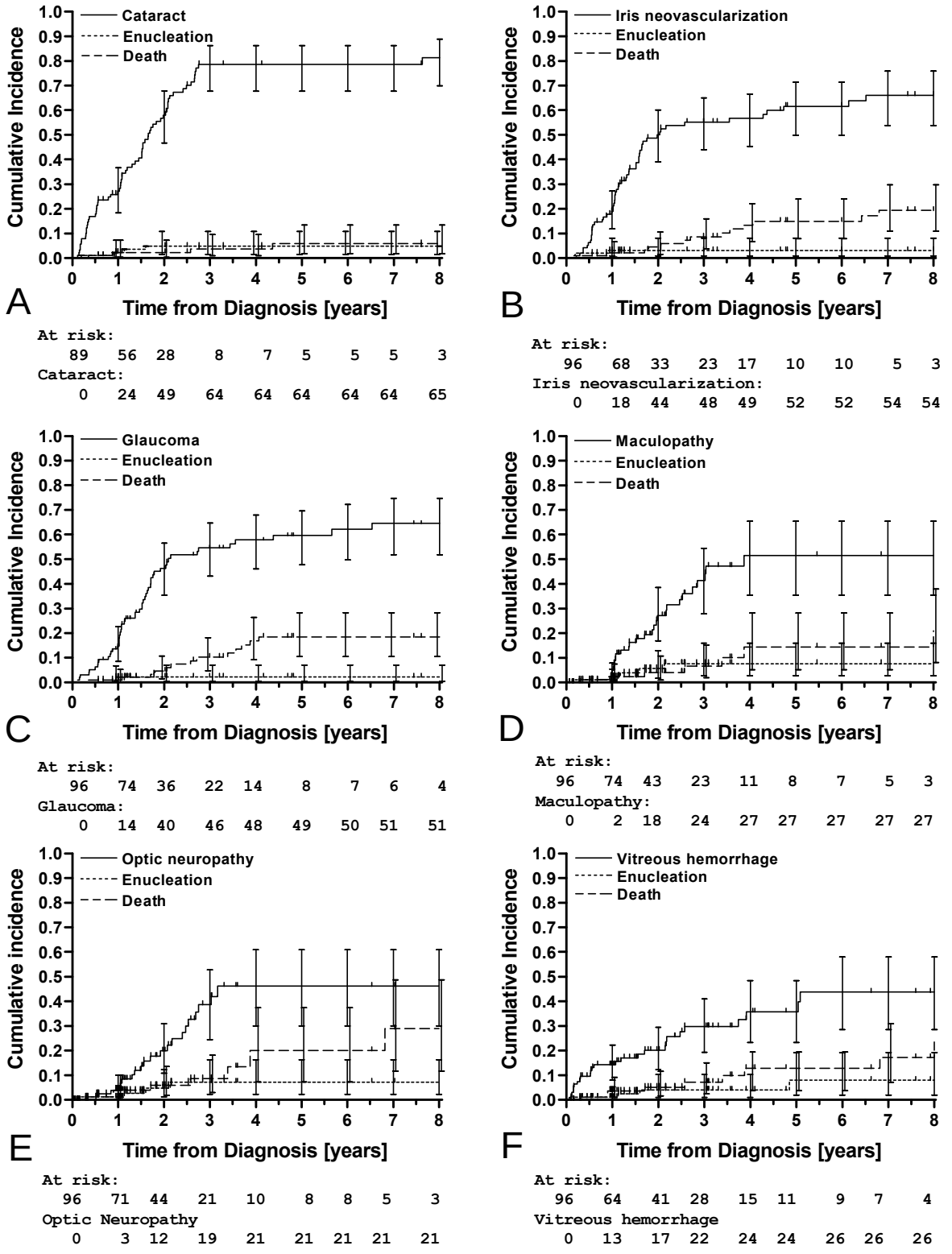

Figure 10. *Cumulative incidence of **A**, development or progression of cataract; **B**, iris neovascularization; **C**, glaucoma; **D**, maculopathy; **E**, optic neuropathy; and **F**, occurrence or recurrence of vitreous hemorrhage after iodine brachytherapy of a large uveal melanoma. Cumulative incidence of secondary enucleation and death, the main competing risks, are also plotted. Bars indicate 95% confidence intervals and ticks show censored observations.*

***Table 5**. Competing risks regression of time to complication after iodine-125 brachytherapy of 96 patients with a uveal melanoma large by the Collaborative Ocular Melanoma Study criteria*

Variable	Coefficient (SE)	Wald chi-square	*P*	Hazard ratio (95% CI)
Cataract				
Tumor height*	0.204 (0.073)	7.75	0.005	1.23 (1.06 - 1.42)
Age†	-0.015 (0.010)	1.00	0.15	0.99 (1.01 - 0.96)
Diabetes‡	0.578 (0.624)	1.00	0.35	1.78 (0.57 - 5.54)
Iris neovascularization				
Tumor height*	0.147 (0.087)	2.89	0.089	1.16 (0.98 - 1.37)
RD at diagnosis‡	0.557 (0.372)	2.23	0.14	1.74 (0.84 - 3.62)
Diabetes‡	0.558 (0.762)	0.54	0.46	1.75 (0.39 - 7.78)
Glaucoma				
RD at diagnosis‡	0.776 (0.413)	3.52	0.061	2.17 (0.97 - 4.88)
IOP at diagnosis¶	0.081 (0.041)	3.92	0.048	1.08 (1.00 - 1.17)
Maculopathy (tumors located ≥2 mm from fovea)				
Distance to fovea*	-0.133 (0.055)	5.88	0.015	0.88 (0.79 - 0.97)
Age†	-0.021 (0.018)	1.33	0.25	0.98 (0.95 - 1.01)
Optic neuropathy				
Distance to disc*	-0.1041 (0.055)	3.57	0.059	0.90 (0.81 - 1.00)
Diabetes‡	0.6075 (1.103)	0.30	0.58	1.84 (0.21 - 15.95)
Vitreous hemorrhage				
VH at diagnosis‡	0.975 (0.531)	3.38	0.066	2.65 (0.94 - 7.51)
Tumor LBD*	0.067 (0.060)	1.23	0.27	1.07 (0.95 - 1.20)
Persistent retinal detachment				
Tumor height*	0.268 (0.127)	4.46	0.035	1.31 (1.02 - 1.68)
Ciliary body involvement‡	-0.339 (0.491)	0.48	0.49	0.71 (0.27 - 1.87)

SE = Standard error, CI = Confidence interval, RD = Retinal detachment, IOP = Intraocular pressure, VH = Vitreous hemorrhage, LBD = Largest basal diameter

* continuous variable, mm

† continuous variable, years

‡ coding no=0, yes=1

¶ continuous variable, mmHg

6.1.8.3. Iris Neovascularization and Glaucoma

The cumulative incidence of iris neovascularization was 62% (95% CI, 50%-71%) at 5 years (Fig.10B). In Cox proportional hazards regression modeling with simulated dose distribution, iris neovascularization was associated with dose to the opposite retina in the 87 eyes for which this variable was applicable (HR 1.72 for each 10 Gy increase, P=0.018), but unassociated with dose to chamber angle and dose rate at all points measured. In trivariate models, dose to the opposite retina (Table 6) and tumor height provided a similar fit.

Table 6. *Cox proportional hazards regression of time to complication after iodine-125 brachytherapy of 96 patients with a uveal melanoma large by the Collaborative Ocular Melanoma Study criteria*

Variable	Coefficient (SE)	Wald chi-square	*P*	Hazard ratio (95% CI)
Cataract				
Dose to lens center*	0.138 (0.044)	9.67	0.002	1.15 (1.05 - 1.25)
Age†	0.006 (0.011)	0.29	0.59	1.01 (0.98 - 1.03)
Diabetes‡	0.134 (0.600)	0.05	0.82	1.14 (0.35 - 3.71)
Iris neovascularization				
Dose to opp. retina*	0.056 (0.023)	5.81	0.016	1.76 (1.11 - 2.77)
RD at diagnosis ‡	0.447 (0.420)	1.12	0.29	1.56 (0.69 - 3.56)
Diabetes‡	0.718 (0.759)	0.90	0.34	2.05 (0.46 - 9.08)
Glaucoma				
Dose to opp. retina*	0.736 (0.325)	5.11	0.024	2.09 (1.10 - 3.95)
Tumor height§	-0.038 (0.110)	0.12	0.73	0.96 (0.78 - 1.19)
IOP at diagnosis‖	0.070 (0.047)	2.19	0.14	1.07 (0.98 - 1.18)
Maculopathy (tumors located ≥2 mm from fovea)				
Dose to fovea*	-0.008 (0.007)	1.21	0.27	0.99 (0.98 - 1.01)
Distance to fovea§	-0.178 (0.073)	5.90	0.02	0.84 (0.73 - 0.97)
Optic neuropathy				
Dose to disc*	0.062 (0.031)	4.12	0.042	1.06 (1.00 - 1.13)
Distance to disc§	-0.079 (0.063)	1.61	0.20	0.92 (0.82 - 1.04)

SE = Standard error, CI = Confidence interval, IOP = Intraocular pressure
* continuous variable, 10 Gy
† continuous variable, years
‡ coding no=0, yes=1
§ continuous variable, mm
‖ continuous variable, mmHg

The IOP was over 24 mmHg in 6 (6%) tumor eyes at diagnosis. Cumulative incidence of glaucoma developing after IBT was 60% (95% CI, 48%-70%) at 5 years (Fig.10C). Of 51 glaucomas, 43 (84%) were neovascular, 5 (10%) secondary angle-closure, and 3 secondary open-angle (possibly from scarring of the nearby chamber angle after IBT) in type. Of the 54 patients with iris neovascularization, 39 (72%) developed neovascular glaucoma. The prevalence of IOP over 24 mmHg was 39% (95% CI, 20%-59%) at 5 years after IBT, and it remained fairly constant between 2 and 6 years from treatment (Fig.2B in II).

By univariate competing risks regression, IOP at diagnosis (P=0.10) and preoperative exudative RD (P=0.094) were associated with time to glaucoma. Both increased in significance when combined in a bivariate model (Table 5). In Cox regression models with simulated dose distribution, secondary glaucoma was associated with dose to the opposite retina (HR 1.90 for each 10 Gy increase, P=0.025), even when adjusted for tumor height and IOP at diagnosis (P=0.024, Table 6).

Treatment of glaucoma after IBT is detailed in Study II. Briefly, glaucoma patients were managed with medication and six (12% of all patients with glaucoma) underwent transscleral contact krypton[142] or red diode laser[223] cyclophotocoagulation. Filtration surgery was considered contraindicated. Eyes with light perception or worse vision were managed with topical mydriatics and corticosteroids or with cyclophotocoagulation to provide symptomatic relief in patients who wished to avoid secondary enucleation.[142;223] Six (12%) of the 51 eyes which developed glaucoma after IBT underwent secondary enucleation because of pain unresponsive to therapy. All enucleated eyes had light perception or worse vision.

The risk for these complications appears to be influenced by multiple factors that are not directly related to radiation, but which may contribute to ischemia of the ocular tissues. Iris neovascularization can develop even in eyes with untreated large tumors.[230;258] Large tumor size is reported to predict NVG after IBT, but only tumor height was associated with iris neovascularization and neither height nor LBD were associated with secondary glaucoma in the present study. However, dose to the opposite retina which was associated with glaucoma reflects both the total irradiated volume and the height of the tumor. This association can be due to the heavier radiation burden to the eye as a whole or to the larger tumor mass later to undergo necrosis, or both.

Glaucoma and iris neovascularization are reported to be more frequent complications of brachytherapy if the anterior part of the tumor involves the iris,[118] but such tumors were ineligible. That the radiation dose to the chamber angle was not associated with either iris neovascularization or glaucoma seems to indicate that the association between anterior location of the tumor and these outcomes is not explained by direct radiation damage to the anterior segment alone.

The results support an association between chronic RD, iris neovascularization,[98] and glaucoma. In addition, development of secondary glaucoma in this data set was associated with IOP at diagnosis, suggesting that host susceptibility may influence the risk of glaucoma developing.

Iris neovascularization and subsequent glaucoma are a leading cause of secondary enucleation of eyes where the tumor has been adequately controlled by radiotherapy.[78;108;200;256] It is also likely that they account for much of the vision loss in eyes where radiation optic neuropathy and maculopathy have been avoided. Means to prevent neovascular glaucoma after IBT, for example by reducing ocular ischemia and by promoting resorption of RD[23;98] should be investigated further. Laser-induced hyperthermia of the tumor at the time of IBT[45] and, in selected cases, resection of the leaking irradiated tumor (Bertil Damato, unpublished observation) might prove useful in preventing chronic RD.

6.1.8.4. Maculopathy

The 5-year cumulative incidence of maculopathy was 52% (95% CI, 35%-65%; Fig10D). Univariate competing risks regression, limited to the 80 eyes in which the distance of the posterior tumor margin from the foveola was 2 mm or more, identified distance to foveola (P=0.015) and gender (P=0.032) as factors associated with time to maculopathy. Both retained significance when combined in a bivariate model and in bivariate models which included age or diabetes as a confounding factor (Table 5).

There were 40 men and 40 women in the analysis of which 18 and seven, respectively, developed maculopathy. The present study provides no explanation for this association, which could have occurred by chance. On the other hand, environmental factors such as cigarette smoking and underlying conditions such as systemic hypertension in which there is a possible difference between the genders, were not analyzed.

Maculopathy developed in one patient when the dose to the macula was less than 40 Gy or the T:M ratio was more than 2.0, and to five patients when the dose was less than 50 Gy (Fig.4D,E in III). A statistical association between time to maculopathy and dose to (P=0.47), or dose rate at (P=0.34), the center of the macula was not evident in Cox regression models. Distance of the posterior tumor margin to the center of the fovea was significantly associated with development of maculopathy, even when adjusted for dose to the macula (HR 0.84 for each 1 mm increase, P=0.015; Table 6).

Lack of a significant association between maculopathy and dose to the center of the macula was contrary to some reports.[37;116] Radiation maculopathy results from damage to vessels which course around the macula to feed the foveal area. These vessels may receive much larger doses than the fovea itself.[116] After proton beam therapy, the risk for maculopathy was reported to level off after a radiation exposure of 40 Gy to the fovea.[116] The

vast majority, or 84 of our patients, received at least this dose, weakening the possibility of confirming an association between dose and maculopathy, should the same nonlinear relationship apply to IBT. Moreover, some large melanomas can damage the macula irrespective of radiation both directly and through exudative RD. Furthermore, the fact that dose to the macula was strongly associated with loss of vision after IBT suggests that there may be potential bias in assessing macular damage: many eyes were censored from analysis after visibility to the fundus was lost and many of these had large macular doses.

Even though the risk for radiation maculopathy may not be as directly dose-related as optic neuropathy, limiting macular dose by treatment planning and plaque design is justified. A suggested aim could be keep the macular dose as much under 40 Gy as possible without compromising local control. If maculopathy develops, intravitreal triamcinolone[248] with or without retinal photocoagulation[141;157] may improve visual outcome at least in the short term. It would be useful to know whether macular doses under 40 Gy correlate with the severity of macular damage and its responsiveness to these treatments.

6.1.8.5. Optic Neuropathy

Cumulative incidence of optic neuropathy was 46% (95% CI, 30%-61%; Fig.10E) at 5 years. Optic neuropathy developed in two patients when the dose to the optic disc was less than 50 Gy or the T:D ratio was more than 1.5 (Fig.4F,G in III). Patients with a T:D ratio less than 1 were 4 times as likely to develop optic neuropathy as those with a higher ratio (HR 4.37, P=0.004).

Univariate competing risks regression identified two interrelated clinical factors, distance to optic disc (P=0.015) and ciliary body involvement (P=0.0024), to be associated with optic neuropathy. Distance to disc, chosen for bivariate models, remained significant when adjusting for diabetes (HR 1.84, Table 5) or tumor height (data not shown).

Both tumor height and distance between the tumor and optic disc can act as surrogate variables for dose to the optic disc. Indeed, in a bivariate Cox regression model which included simulated dose to the optic disc, distance to disc lost significance (Table 6). Both dose (HR 1.08 for each 10 Gy increase, P=0.001) and dose rate (HR 1.06 for each 10 cGy/h increase, P=0.002) at the optic disc were strongly associated with this complication at the univariate level.

The data suggest that the tolerance of the optic nerve for IBT was between 40 Gy and 60 Gy, in agreement with reports concerning optic neuropathy after other types of irradiation,

which have suggested a threshold of 30 to 50 Gy.[36;116;147;176] The sensitivity of the optic nerve to high dose rates has also been documented by others.[36;119]

Because optic neuropathy often causes severe and irreversible vision loss and no effective treatment is currently available, reducing dose to the optic disc should be a high priority in treatment planning. This is routinely done in charged particle therapy planning but should be included in the IBT protocol by using conformal seed placement and collimating plaque design when necessary. Tumors touching the optic disk are a particular problem, because even the most effective collimation is unlikely to lower the dose to tolerable levels while maintaining adequate tumor dose to prevent recurrence.

6.1.8.6. Persistent Exudative Retinal Detachment

Exudative RD was present in 58 (61%) eyes at diagnosis and an additional 23 eyes had subretinal fluid over and around the tumor. The RD resolved within 6 months in 42 (72%) of the 58 eyes, and 19 eyes had or developed a RD which persisted for more than six months. The 5-year incidence of persistent or progressive RD was 25% (95% CI, 15%-36%). The proportion of patients with RD decreased from 31% (95% CI, 20-44) at 1 year to 13% after 5 years from IBT (Fig.2D in II).

Tumor height was associated with time to persistent RD in a univariate CRR model (P=0.046). In bivariate models, it retained significance (HR 1.31 for each mm increase, P=0.035) when adjusted for ciliary body involvement (HR 0.71, Table 5) and LBD (data not shown), two factors associated with risk of RD in eyes with uveal melanoma.[159] Substituting tumor height with dose to the opposite retina in a bivariate Cox proportional hazards regression model with ciliary body involvement did not improve the fit of the model.

Large LBD is associated with an increased, and ciliary body involvement with a decreased, risk of RD in eyes with unselected, untreated uveal melanoma.[159] These two associations were present but not statistically significant in the present data set, possibly because a substantial part of a large melanoma that involves the ciliary body extends to the choroid and can leak under the retina.

It should be remembered that persistent or recurrent retinal detachment after radiotherapy of a uveal melanoma can be a sign of disease activity.[35;105;127;257] Even in cases where local control has been achieved, persistent RD threatens vision and can predispose to neovascular glaucoma.[78;98;143] Unfortunately, the present study does not suggest any new means to limit this complication. A study of medium-sized tumors suggested more rapid

resolution of RD after pre-irradiation laser-induced hyperthermia.[45] Managing all large choroidal melanomas with laser or TTT before IBT may be impractical, however, especially when many present with extensive RD at diagnosis. Removing the leaking tumor mass by transvitreal endoresection in selected cases looks promising but the safety of this procedure is yet to be established.[29]

6.1.8.7. Vitreous hemorrhage

Vitreous hemorrhage was present in 13 (14%) eyes at diagnosis. The cumulative incidence of vitreous hemorrhage at 5 years after IBT was 36% (95% CI, 23-48%; Fig.10F). The prevalence of vitreous hemorrhage after IBT fluctuated between 20% and 50% long term (Fig.2C in II).

Vitreous hemorrhage present at diagnosis was associated with time to postoperative vitreous hemorrhage in univariate competing risks regression (P=0.051) and in a bivariate regression model that included tumor LBD (Table 5), but it lost significance when adjusted for the presence of a break in Bruchs membrane (data not shown). Postoperative vitreous hemorrhage was not associated with any dose or dose rate analyzed.

In general, uveal melanomas which give rise to vitreous hemorrhage invade the retina.[146] It was impossible to reliably assess which patients had such a tumor because the presence of this feature had not been assessed prospectively. It is unlikely that vitreous hemorrhage after IBT can be influenced by treatment planning. Severe bleeding which compromises visibility to the fundus and hinders vision can be cleared with post-treatment vitrectomy.

6.1.9. Extrapolated Response Dose

Optic neuropathy and blindness, which were strongly associated with dose to the optic disc and dose to the macula, respectively, were also associated with corresponding ERD, but the association was weaker. In all other analyses, substituting dose with ERD resulted in loss of a significant association with the outcome of interest, if present.

High dose rates are thought to be more damaging to late-reacting normal tissues than to tumor cells. This effect increases with increasing irradiated volume,[126] which was large in this study. ERD was designed to take tissue susceptibility and dose rate effect into account.[62] The lack of association between dose rate and ocular complications other than optic neuropathy, and the fact that ERD was not superior to BPS dose in regression analysis, was unexpected. However, the dose rate effect is reported to be less pronounced at rates of 60

cGy/h or less,[125] and more than half of the eyes in the present data set received an apical dose rate lower than this. In support of this possibility, a study of smaller melanomas, which reported a comparable mean macular dose (98 Gy vs. 101 Gy in the present study) but much higher mean macular dose rate (139 cGy/h vs. 82 cGy/h), found the dose rate at the macula to be more strongly associated with vision loss than dose to the macula and optic disc.[148] At least with the relatively low dose rates of the present study, ERD does not provide any additional prognostic information compared to delivered dose alone. It would be interesting to see if ERD would be of more value in assessing high-dose-rate treatment such as Strontium-90 brachytherapy.

6.1.10. Simulated Treatment with Collimating Plaques

Simulated treatments with collimating plaques and standard prescription doses graded according to tumor height were modeled for 77 patients (58 managed with CCC and 19 with CCB plaques). These models suggested a median decrease of 36 Gy (range, 19 Gy increase to 198 Gy decrease) in dose to the center of the macula and a median decrease of 30 Gy (range, 9 Gy increase to 160 Gy decrease) in dose to the optic disc, when compared to the BPS doses of the actual treatments (Fig.11A). The median T:D and T:M ratios, based on these 77 patients, improved from 0.94 (range, 0.39-3.15) to 1.61 (range, 0.35-5.27) and from 0.99 (range, 0.27-2.59) to 1.81 (range, 0.36-4.04), respectively (Fig.11B).

Of 69 patients whose BPS dose to the macula had exceeded 50 Gy, 45 (65%) avoided this level of radiation in the simulation with collimating plaques, and 23 (38%) of 60 patients avoided a 50 Gy dose to the optic disc (Fig.11B). This analysis confirmed that small changes in plaque design may notably reduce radiation dose to the optic nerve, macula, and other tissues adjacent to the tumor, increasing the therapeutic ratio without compromising tumor dose. As a downside, such collimating plaques will require absolute safety margins. Despite collimation, doses still exceeded the suggested tolerance limits in many patients.

The reduction in doses to the macula and optic disc achieved with collimating plaques was, in some patients, partly due to the standard prescription dose graded by tumor height, so that very thick tumors received 60 to 70 Gy instead of 80 to 100 Gy in the simulation, as has been the practice in the study center more recently. The improvement in T:M and T:D ratios, however, reflects the benefit from plaque redesign only.

Favorable theoretical dose distributions have been reported with plaques in which each source is individually collimated.[12] Ensuring an adequate dose to the entire tumor base

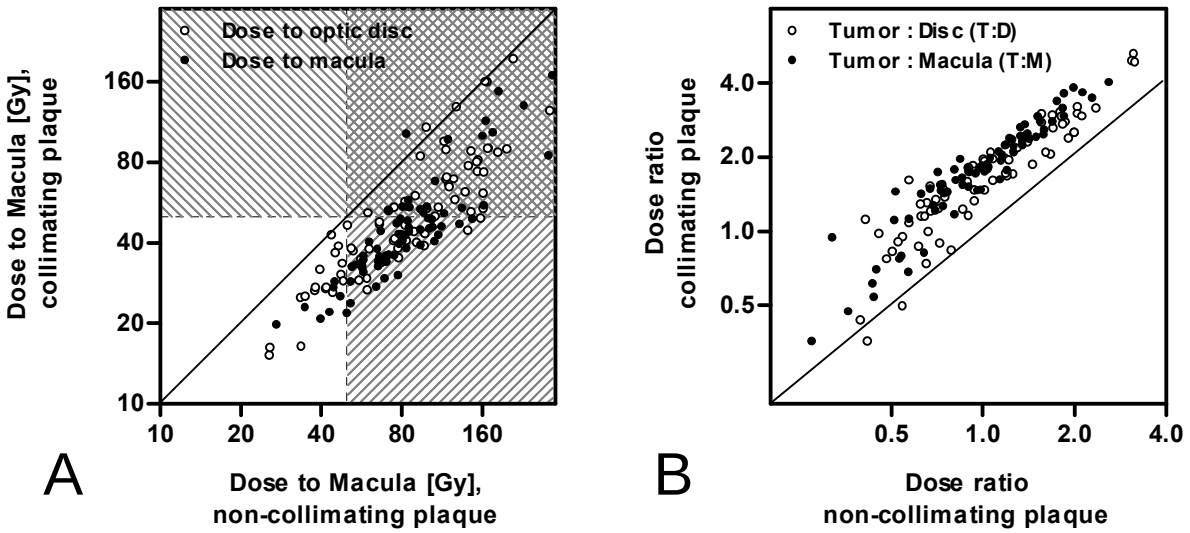

Figure 11. *Plot of (**A**) dose delivered to the optic disc and macula using the original non-collimating plaques (x-axis) vs. the prototype collimating plaques (y-axis) in the simulated treatment of 77 patients with a large uveal melanoma. Solid line indicates no difference in dose. Dotted lines indicate proposed 50 Gy thresholds of increased risk for complications. (**B**) Similar plot using Tumor:Disc and Tumor:Macula dose ratios (also known as therapeutic ratios). Solid line indicates no difference in therapeutic ratio and dots falling above this indicate patients in which the collimation improved the threapeutic ratio.*

and underlying sclera using individually collimated seeds would require the use of an increased number of seeds of correspondingly lower intensity. Although a more radical redesign would have further decreased the dose to tissues immediately adjacent to the plaque edge, this zone less frequently extends to the macula and optic disc and it acts as a safety border against marginal tumor recurrence. Furthermore, as one of the goals of this study was to serve as a pilot for a prospective study of the collimating plaque design, it was reasonable to conform as much as possible to the existing brachytherapy plaques and protocol.

By using a treatment planning software capable of detailed three-dimensional modeling of the dose volume and the tumor eye and applicators with collimated seeds, it seems possible to achieve more control over the irradiated volume in brachytherapy.

6.1.11. Strengths and Limitations

A clear strength of the present study is that it was carried out with a population-based data set of consecutive patients managed in a national referral center that manages more than 90% of uveal melanomas in the Finnish population. It is safe to say that the present series is currently the largest reported population-based data set of patients with COMS Large melanomas managed with an eye-conserving treatment. Another advantage is the availability of prospectively collected and detailed patient records from both the study center and regional hospitals which left just a few patients lost to follow-up and very few gaps in the data.

Furthermore, the present study was able to reliably assess the causes of death in the majority of deceased patients using histopathology samples instead of relying on death certificates in which the possibility of late-metastasing malignancy such as uveal melanoma is sometimes overlooked.[164]

A marked limitation of the present study is that it failed to prospectively address the quality-of-life aspects after treatment, and such an analysis was no longer feasible without introducing bias because many patients had died. Although most follow-up data have been prospectively collected, some events of interest, such as persistence of RD, had to be re-assessed by reviewing the patient records. A small proportion of patients had missing data, and not all complications could be reliably assessed after visibility to the fundus was compromised. The latter problem was taken into account by censoring patients from analysis at that point.

A BPS simulation depends on the accuracy of clinical examination and, in retrospective studies, on the quality of patient records. The position of the plaque in the model cannot be completely controlled retrospectively, and the results should thus be interpreted with caution until confirmed by prospective studies. Using extraocular muscles and limbus as landmarks, retrospective positioning of the plaque with little ambiguity was found to be possible in the majority of cases, with sufficient accuracy to suggest unobserved tilting of some posteriorly placed plaques from the scleral surface along the optic nerve. Sensitivity analysis suggested that the retrospective BPS doses to the tumor apex reported in the present study should be essentially unaffected by error in placement of the seeds and the plaque in the model, and that the simulated mean doses to the lens, macula and optic disc are unlikely to deviate more than 5 Gy from the actual mean doses. The BPS off-axis doses are also subject to up to 11% deviation due to mathematical approximations used by the software; in general this error is reported to be 5% or less.[162]

6.2. Transscleral Local Resection vs. Iodine Brachytherapy for Uveal Melanomas that are Large Because of Tumor Height (IV)

6.2.1. Baseline Population Characteristics

The median age of patients was 46 years (range, 21-73) in the TSR arm and 66 (range, 35-85) in the IBT arm. TSR was rarely given to patients older than 60 years, whereas 67% of IBT patients were in this age group. Because of differences in health care systems, total follow-up times were notably shorter in the TSR arm (median, 2.3 vs. 5.3 years; P=0.0002 Kruskal-Wallis test). The center-related difference in follow-up times is unlikely to be a major source of bias, because visual loss and the majority of complications analyzed occur within the first three years after either treatment (II).[27;158] Cumulative incidence analysis and competing risks regression also take the varying lengths of follow-up appropriately into account.

6.2.2. Baseline Tumor Characteristics

The tumors tended to be thicker in the TSR arm (median height, 11.0 mm; range, 8.0-14) as compared to the IBT arm (median, 10.6 mm; range, 8.2-13.3; P=0.086). There was no difference in the distribution of LBD (P=0.20), the median of which was 12.9 mm (range 9.8-16) in the TSR arm and 14.0 mm (range, 7.3-16) in the IBT arm (Fig.4B).

The anterior tumor margin involved the ciliary body in 24% of TSR patients and in 39% of those managed with IBT (P=0.24, Fishers' exact test, two-sided). The posterior tumor margin extended to within 2 mm of the optic disc in no eye managed with TSR as compared to 39% of the eyes managed with IBT (P=0.017) and 24% vs. 20% of tumors were located within 2 mm of the fovea (P=0.79), respectively (Fig.4D).

Differences in tumor size and patient age at baseline were adjusted for in the regression models. In most models, including the baseline confounders strengthened the association between treatment type and the outcome of interest.

6.2.3. Preservation of Visual Acuity

At baseline 11 patients (33%) in the TSR arm and 18 patients (33%) in the IBT arm had VA better than 20/70. The 2-year cumulative incidence of losing 20/70 vision was 90% (95% CI, 47-99) in the TSR arm and 89% (95% CI, 62-97) in the IBT arm. (Table 7). All IBT patients lost this level of vision in the tumor eye within 30 months but one regained it after cataract

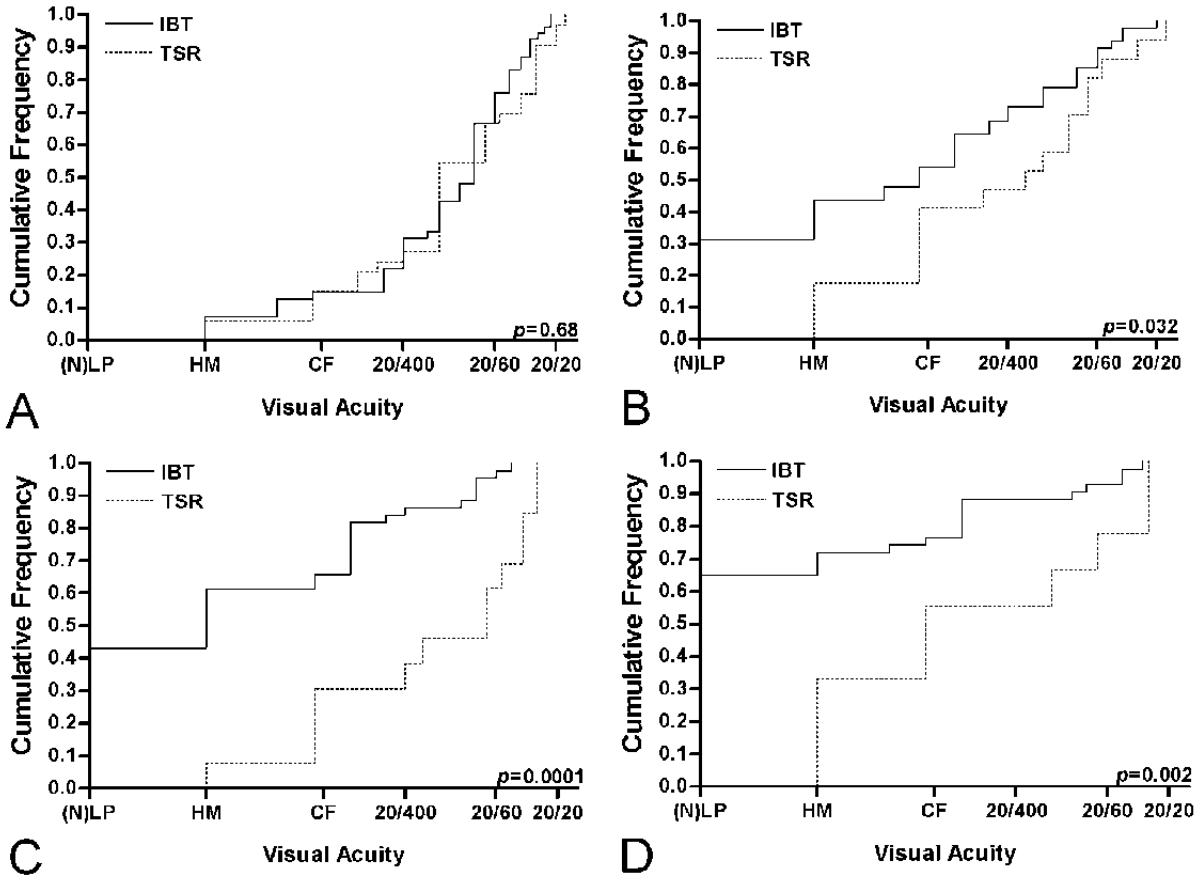

Figure 12. *Cumulative frequency distribution of visual acuity at* ***A****, baseline;* ***B****, 1 year;* ***C****, 2 years; and* ***D****, 3 years after treatment of 33 patients managed with transscleral local resection (TSR) and 54 patients managed with iodine brachytherapy (IBT), who had a uveal melanoma large by the COMS criteria only because of its height. Kruskal-Wallis test.*

surgery. One patient in the TSR arm retained this level of VA (Fig.3A in IV) for at least 4 years.

Baseline VA of the tumor eye was better than 20/400 in 25 patients (75%) in the TSR arm and in 42 patients (78%) in the IBT arm. After TSR, the cumulative incidence of loss of VA 20/400 was 53% (95% CI, 31-71) at 1 and 60% (95% CI, 35-77) at 2 and 3 years (Fig.3B in IV). After IBT, the corresponding incidences were 60% (95% CI, 44-73), 75% (95% CI, 59-86) and 91% (95% CI, 76-97).

The mean VA after TSR was 20/320 to 20/640 throughout the first 5 years and approximately one line better than the mean VA after IBT, which varied between 20/640 and 20/1250 (Fig.3C in IV).

The cumulative frequency of VA levels in the treatment arms was comparable at baseline (P=0.68) but at 1, 2, and 3 year time points showed a statistically significant difference between the arms. The proportion of patients with low VA increased with time in both groups, but the effect was smaller in the TSR arm (Fig.12).

A multivariate logistic regression model was used to adjust for baseline VA, age, and H:D ratio. Treatment with TSR was not consistently associated with avoiding loss of 20/70 vision. Treatment with TSR was independently predictive of avoiding loss of VA 20/400 at 1, 2, and 3 years, with the largest difference present at 2 years (P=0.005, Table in IV).

Better preservation of vision up to three years from the time of treatment was evident in all three different types of analysis. Cumulative incidence of blindness, which evaluates the timing of vision loss but lacks the ability to account for recovery of lost vision, suggests that few new cases of blindness occur one year after TSR whereas the incidence after IBT steadily increases. TSR was also associated with preservation of reading vision at two years but this finding was not statistically significant at other assessed time points, possibly because of a smaller difference and fewer patients at risk.

6.2.4. Local Tumor Recurrence

Local tumor recurrence developed in nine patients managed with TSR and in three managed with IBT. The 5-year cumulative incidences of local recurrence were 41% (95% CI, 17-63) and 7% (95% CI, 2-17), respectively (Fig.5A in IV). The 5-year recurrence rate was 37% (95% CI, 7-66) in the TSR subgroup that received adjuvant irradiation treatment and 46% (95% CI, 13-74) in the subgroup that did not. When comparing only those TSR patients who received adjuvant radiotherapy with IBT, treatment with TSR was still statistically the most significant risk factor for recurrence (P=0.023; CRR).

Of the nine patients with recurrence after TSR, six were managed with secondary irradiation (three with RuBT and four with PBT), one with transpupillary thermotherapy, and two underwent enucleation. Three of the patients managed with secondary radiotherapy experienced a second relapse, and underwent enucleation. Two of the three patients with local tumor recurrence after IBT were managed with secondary IBT and one underwent secondary enucleation.

More frequent local recurrence has not been linked to higher mortality after TSR as compared to IBT.[158] Because recurrence after TSR usually results from tumor margins that were not clear, it may not reflect increased malignancy of the tumor.[53] The 5-year recurrence rate was not higher than in eyes with smaller tumors,[27;71;158] and the results are improving with refinements of surgical technique.[67;71] A greater risk of local recurrence nevertheless remains a drawback of TSR and must be weighed against the prospect of avoiding blindness in the tumor eye.

6.2.5. Iris Neovascularization and Glaucoma

Iris neovascularization and glaucoma developed only in patients who underwent IBT. The 5-year cumulative incidence of neovascularization was 64% (95% CI, 47-77) and that of glaucoma 62% (95% CI, 45-75; Fig.5C in IV).

6.2.6. Optic Neuropathy

The 5-year cumulative incidences of optic neuropathy were 7% (95% CI, 1-19) and 58% (95% CI, 36-75) after TSR and IBT, respectively (Fig.5E in IV). One of the three TSR patients who developed optic neuropathy received RuBT as adjuvant therapy, but the neuropathy resulted from ocular hypotony; one developed a swollen disc soon after surgery, and the third presented with optic atrophy 7 years after TSR.

Adjusting for distance from posterior tumor margin to the optic disc identified IBT (HR 3.74, P=0.042) as an independent predictor of neuropathy. Optic neuropathy is associated with a radiation dose over 50 Gy to the optic nerve,[116] which was exceeded in 43 (80%) eyes in the IBT arm (III).

The incidences of neovascular glaucoma and optic neuropathy, two major complications of IBT, were low after TSR and not different from previous series of mainly smaller, unselected tumors.[27;158] Avoiding these complications is likely to be the main explanation for better preservation of vision after TSR in the present study.

6.2.7. Persistent Retinal Detachment

RD of more than one quadrant was present at baseline in 25 (76%) and 29 (54%) of the eyes in the TSR and IBT arms, respectively (Fig.5F in IV). New RD after TSR was rhegmatogeneous in type and the 5-year cumulative incidence was 42% (95% CI, 25-59). Of the 14 patients with RD after TSR, nine underwent pars plana vitrectomy, one was managed with a scleral buckling procedure alone, and three patients, all with total RD and no visibility to the fundus, underwent enucleation. After IBT exudative RD persisted or reappeared in 11 patients with a 5-year cumulative incidence of 27% (95% CI, 14-42). The prevalence of RD decreased rapidly and remained under 20% after TSR. The prevalence of RD in the IBT arm also decreased but remained 10-20 percentage points higher (Fig.6A in IV).

Table 7. *Summary of cumulative incidences of loss of 20/70 and 20/400 vision and of complications after iodine brachytherapy (IBT) and transscleral local resection (TSR) of a uveal melanoma classified as large by the Collaborative Ocular Melanoma Study criteria. Tumors eligible to Study IV were classified as large because of tumor height alone.*

	Studies I-III	**Study IV**	
2-year cumulative incidence	IBT	IBT	TSR
Loss of VA 20/70	85% (71-93%)	89% (62-97%)	90% (47-99%)
Loss of VA 20/400	69% (57-78%)	75% (59-86%)	60% (35-77%)
5-year cumulative incidence			
Loss of VA 20/400	84% (73-91%)	95% (76-99%)	68% (40-85%)
Local tumor recurrence	6% (2-12%)	7% (2-17%)	41% (17-63%)
Cataract	79% (68-86%)	78% (62-88%)	91% (68-98%)
Iris neovascularization	62% (50-71%)	64% (47-77%)	0%
Glaucoma	60% (48-70%)	62% (45-75%)	0%
Maculopathy	52% (35-65%)	43% (22-62%)	63% (34-82%)
Optic neuropathy	46% (30-61%)	58% (36-75%)	7% (1-19%)
Retinal detachment	25% (15-36%)	27% (14-42%)	42% (25-59%)
Vitreous hemorrhage	36% (23-48%)	39% (23-55%)	67% (47-80%)

6.2.8. Other Complications

The 5-year cumulative incidences of cataract, maculopathy and vitreous hemorrhage in both treatment arms are shown in Table 7. All three were common after both treatments with competing risks regression showing higher risk for cataract and maculopathy after TSR.

In the TSR arm retinal folds and preretinal fibrosis were found in seven eyes, cystoid macular edema in three eyes, and involvement of the macula by the surgical coloboma in four eyes. Direct scarring and atrophy of the macula was seen in four eyes and radiation retinopathy in eight eyes after IBT. All cases of vitreous bleeding in patients managed with TSR occurred within 6 months of surgery. Ten (48%) hemorrhages resolved spontaneously, seven eyes underwent vitrectomy (six had other indications to surgery as well), and three eyes with persistent vitreous hemorrhage and total RD underwent enucleation. In the IBT arm, one of the 17 patients with vitreous hemorrhage underwent vitrectomy, six hemorrhages spontaneously resolved and 10 persisted throughout follow-up.

Despite the high frequency of these complications after TSR in the present series, preservation of VA was still better than after IBT.[158] Although a detailed analysis of the exact cause of the vision loss was not done, it stands to reason that many patients managed with TSR avoided a profound and permanent loss of vision by avoiding NVG and optic

neuropathy. Vision loss caused by cataract, rhegmatogenous RD or vitreous bleeding can be remedied which leaves maculopathy to account for the relatively frequent loss of reading vision observed.

6.2.9. Number Needed to Treat

Of patients with better than 20/400 vision at diagnosis, 13 in the TSR arm and 38 in the IBT arm were under follow-up for at least 2 years after treatment. Five local tumor recurrences were observed in the TSR arm and two in the IBT arm. In both groups five patients maintained 20/400 vision for at least 2 years (range, 2.5 to 11). The number needed to treat with TSR instead of IBT for one additional patient to gain this benefit was 4.0 (95% CI, NNTB 1.9 - NNTB 570; Fig.7 in IV). The corresponding number to treat with TSR for one more patient to be harmed by local recurrence was 3.0 (95% CI, NNTH 1.7 - NNTH 10.9).

If this estimate based on the present, relatively small data set can be verified in independent, preferably prospective, studies, it may not be advisable to recommend TSR as a first option for patients with uveal melanomas of this size under normal circumstances, i.e. when the fellow eye is healthy and functional. In special situations, when it is imperative to save as much vision as possible and the patient accepts the relatively high risk of local failure, TSR seems the better choice. This conclusion must be re-evaluated when advances in TSR protocol notably reduce the risk of local tumor recurrence.

6.2.10. Strengths and Limitations

TSR and IBT have been compared previously, both by our study centers and by others.[27;158] One of the merits of the present study is that it focuses on the subgroup of tumors that encounter the most problems after IBT and might thus, logically, fare better after TSR. The present study also utilizes cumulative incidence analysis and competing risks regression to factor out the confounding effect of early metastatic death. Finally, the preservation of vision was analyzed using several different methods. By taking repeated loss and recovery of vision and baseline risk factors into account and by estimating the proportion of patients with various degrees of vision loss at different time points, these give a more complete picture of how much vision is saved with TSR. NNT calculations should also prove helpful in considering the benefits and risks associated with these two treatments for uveal melanomas of this size.

Uveal melanomas that are classified as large because of their height are uncommon, making it difficult to organize a prospective study with adequate sample size. The

retrospective setting used in this study may introduce bias in treatment selection, follow-up methods and baseline variables. A two-center design was used to limit selection bias in choosing between the two treatments. This, however, introduced differences in follow-up and in indications for secondary treatment. The different attitude toward secondary enucleation is an obvious source of bias. Eyes managed with TSR in which fundus visibility or vision was lost were enucleated in most cases. After IBT, the policy was to offer enucleation as a safety measure if visibility was lost, but most patients refused this option and preferred to retain the eye for cosmetic reasons (I). This not only makes the comparison of eye retention after the two treatments biased but also risks overestimating any difference in complication rates in favor of TSR. The latter problem was taken into account by censoring enucleated eyes from analysis at the time of enucleation instead of analyzing enucleation as a competing risk. This design produces an overall overestimation of the incidence of complications in both arms by disregarding the fact that patients are no longer at risk of ocular complications after secondary enucleation (II). The inability to detect posterior segment complications after fundus visibility was taken into account by censoring patients from analyses after loss of fundus visibility.

Evolution of the treatment protocols in both study centers during the study period resulted in earlier patients having been managed with a different protocol from the latest. In particular, most later TSR patients received adjunctive RuBT while the earliest did not. It can be argued that this causes internal variation within the TSR group which can affect the outcome. The confounding effect of adjunctive RuBT, if any, should be most evident in local failure after TSR and in the radiation-related complications in eyes where the tumor was located close to the posterior pole. Local failure was less frequent in patients who received adjunctive radiotherapy but still more common than after IBT. Substituting the whole TSR group with only the 20 TSR patients who received adjuvant therapy in the CRR and logistic regression models did not alter the outcome for local recurrence and preservation of vision, the main outcomes of this study.

6.3. Conclusions

In terms of survival, iodine brachytherapy in this series was a safe alternative to enucleation in managing large uveal melanomas. Local tumor control was no worse than with medium-sized tumors and chances to avoid secondary enucleation are good. Unfortunately, side-effects from radiotherapy with the current brachytherapy protocol were frequent, and long-term prognosis of saving usable vision was consequently guarded. Patients with very thick tumors

close to the posterior pole have the highest risk of losing vision after IBT. Patients with ciliochoroidal melanomas had the best chance of maintaining ambulatory vision and are least likely to benefit from enucleation considering the higher risk of early metastatic death associated with tumors involving the ciliary body.

While tumor height was the strongest clinical prognostic factor for vision loss after IBT, dose to the macula and dose to the optic disc were also independently associated with this outcome. Since the means to manage radiation damage to the optic nerve and macula are limited, decreasing the dose absorbed by these critical structures should be a high priority in brachytherapy planning. According to simulations, a clinically meaningful decrease might be achieved by using brachytherapy plaques with appropriate seed collimation and a treatment planning software capable of detailed three-dimensional modeling of the tumor eye and plaque placement.

Even when the risk for optic neuropathy and radiation maculopathy can be decreased by improved plaques and treatment planning, persistent exudative retinal detachment, iris neovascularization and neovascular glaucoma can still cause considerable ocular morbidity and permanent loss of vision. These complications should be anticipated in patients after IBT of a large uveal melanoma and appropriate treatment given as needed. New effective methods of treatment for these conditions as well as evidence-based data of the safety and effectiveness of existing ones should be actively sought.

When discussing treatment of a large uveal melanoma, patients can be informed of available treatment options for their condition and of the risk of vision loss, secondary enucleation, local tumor recurrence and complications associated with each one. In a setting with frequent competing risks, such as early metastatic death, cumulative incidence analysis provides more realistic estimates for this purpose than the Kaplan-Meier method.

If a patient is unwilling to accept the risk of local recurrence and complications associated with IBT of a large uveal melanoma, enucleation can be recommended as an effective and proven treatment. On the other hand, if the clinical setting – such as a blind fellow eye – demands, or the patient himself so prefers, TSR can be considered as an alternative to IBT for tumors that are classified large because of their height in cases when it is imperative to save as much vision as possible. In this case the patient must also be fit enough to undergo hypotensive anesthesia and willing to accept the currently many-fold risk of local tumor recurrence. For patients who do not fulfill these criteria but still prefer to retain

their eye and avoid enucleation, IBT remains a safe option which provides good tumor control and a reasonable cosmetic outcome.

6.4. Future Directions

The encouraging results of the simulated collimating plaque design need to be confirmed with prospective, preferably randomized clinical studies. If found to be suitable for clinical use, such plaques together with accurate and, ideally, conformal treatment planning should increase the number of patients who maintain useful vision after IBT of a large uveal melanoma. In order to avoid a reciprocal increase in local tumor recurrence, these new techniques will demand high precision in plaque placement.

These techniques can potentially be used to improve the already better visual prognosis of IBT for medium-sized melanomas. Further improvement in preserving the eye and vision of patients with a medium to large uveal melanoma managed with any form of radiotherapy can be expected once the underlying reasons for retinal detachment and neovascular glaucoma are better understood and evidence-based means to prevent or manage them are discovered. The high interest in neovascular processes in other fields of ophthalmic and cancer research may help to provide the answers.

Cytogenetic means to identify aggressive uveal melanomas associated with high risk of metastasis would be a major breakthrough not only for assessing survival prognosis and investigating new means to battle metastasis, but also for choosing primary treatment for tumors which are associated with high risk of ocular morbidity after radiotherapy. It then might be even more justified to use local resection, either transscleral or transvitreal, to manage the less aggressive melanomas with less fear of compromising survival.

It is likely that radiotherapy will remain the main eye-conserving option for many large uveal melanomas. The void in controlled studies on managing main radiation-related complications that limit visual results should be filled with prospective studies, such as comparing intravitreal triamcinolone and photodynamic therapy for radiation maculopathy.

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8. References

1. Abramson DH, Schefler AC. Transpupillary thermotherapy as initial treatment for small intraocular retinoblastoma: technique and predictors of success. *Ophthalmology* 2004;111:984-91.

2. Adams KS, Abramson DH, Ellsworth RM, Haik BG, Bedford M, Packer S et al. Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates. *Br J Ophthalmol* 1988;72:494-7.

3. Ah-Fat FG, Damato BE. Delays in the diagnosis of uveal melanoma and effect on treatment. *Eye* 1998;12:781-2.

4. Altman DG. Practical Statistics for Medical Research, 1st ed. London: Chapman & Hall, 1991.

5. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.

6. Amdur RJ, Bedford JS. Dose-rate effects between 0.3 and 30 Gy/h in a normal and a malignant human cell line. *Int J Radiat Oncol Biol Phys* 1994;30:83-90.

7. Apple DJ, Goldberg MF, Wyhinny G, Levi S. Argon laser photocoagulation of choroidal malignant melanoma. Tissue effects after a single treatment. *Arch Ophthalmol* 1973;90:97-101.

8. Archer DB, Amoaku WM, Gardiner TA. Radiation retinopathy--clinical, histopathological, ultrastructural and experimental correlations. *Eye* 1991;5 (Pt 2):239-51.

9. Astrahan MA. A patch source model for treatment planning of ruthenium ophthalmic applicators. *Med Phys* 2003;30:1219-28.

10. Astrahan MA, Luxton G, Jozsef G, Kampp TD, Liggett PE, Sapozink MD et al. An interactive treatment planning system for ophthalmic plaque radiotherapy. *Int J Radiat Oncol Biol Phys* 1990;18:679-87.

11. Astrahan MA, Luxton G, Jozsef G, Liggett PE, Petrovich Z. Optimization of ^{125}I ophthalmic plaque brachytherapy. *Med Phys* 1990;17:1053-7.

12. Astrahan MA, Luxton G, Pu Q, Petrovich Z. Conformal episcleral plaque therapy. *Int J Radiat Oncol Biol Phys* 1997;39:505-19.

13. Augsburger JJ. Is observation really appropriate for small choroidal melanomas. [Review] [69 refs]. *Trans Am Ophthalmol Soc* 1993;91:147-68.

14. Augsburger JJ. Size classification of posterior uveal malignant melanomas. In: Laibson PR. Yearbook of Ophthalmology 1993. St.Louis: Mosby, 1993:155-65.

15. Augsburger JJ, Affel LL, Benarosh DA. Ultrasound biomicroscopy of cystic lesions of the iris and ciliary body. *Trans Am Ophthalmol Soc* 1996;94:259-71.

16. Augsburger JJ, Correa ZM, Freire J, Brady LW. Long-term survival in choroidal and ciliary body melanoma after enucleation versus plaque radiation therapy. *Ophthalmology* 1998;105:1670-8.

17. Augsburger JJ, Gamel JW, Shields JA. Cobalt plaque radiotherapy versus enucleation for posterior uveal melanoma: comparison of survival by prognostic index groups. *Trans Am Ophthalmol Soc* 1989;87:348-59.

18. Augsburger JJ, Golden MI, Shields JA. Fluorescein angiography of choroidal malignant melanomas with retinal invasion. *Retina* 1984;4:232-41.

19. Augsburger JJ, Gonder JR, Amsel J, Shields JA, Donoso LA. Growth rates and doubling times of posterior uveal melanomas. *Ophthalmology* 1984;91:1709-15.

20. Augsburger JJ, Khouri L, Roumeliotis A, Kersten RC, Kulwin DR, Schneider S. Enucleation versus preservation of blind eyes following plaque radiotherapy for choroidal melanoma. *Can J Ophthalmol* 2004;39:372-9.

21. Augsburger JJ, Lauritzen K, Gamel JW, DeBrakeleer DJ, Lowry JC, Eisenman R. Matched group study of surgical resection versus cobalt-60 plaque radiotherapy for primary choroidal or ciliary body melanoma. *Ophthalmic Surg* 1990;21:682-8.

22. Augsburger JJ, Mullen D, Kleineidam M. Planned combined I-125 plaque irradiation and indirect ophthalmoscope laser therapy for choroidal malignant melanoma. *Ophthalmic Surg* 1993;24:76-81.

23. Augsburger JJ, Roth SE, Magargal LE, Shields JA. Panretinal photocoagulation for radiation-induced ocular ischemia. *Ophthalmic Surg* 1987;18:589-93.

24. Augsburger JJ, Schneider S, Freire J, Brady LW. Survival following enucleation versus plaque radiotherapy in statistically matched subgroups of patients with choroidal melanomas: results in patients treated between 1980 and 1987. *Graefes Arch Clin Exp Ophthalmol* 1999;237:558-67.

25. Augsburger JJ, Shields JA. Fine needle aspiration biopsy of solid intraocular tumors: indications, instrumentation and techniques. *Ophthalmic Surg* 1984;15:34-40.

26. Bakri SJ, Sculley L, Singh AD. Imaging techniques for uveal melanoma. *Int Ophthalmol Clin* 2006;46:1-13.

27. Bechrakis NE, Bornfeld N, Zoller I, Foerster MH. Iodine 125 plaque brachytherapy versus transscleral tumor resection in the treatment of large uveal melanomas. *Ophthalmology* 2002;109:1855-61.

28. Bechrakis NE, Foerster MH, Bornfeld N. Biopsy in indeterminate intraocular tumors. *Ophthalmology* 2002;109:235-42.

29. Bechrakis NE, Hocht S, Martus P, Kreusel KM, Heese J, Foerster MH. [Endoresection following proton beam irradiation of large uveal melanomas]. *Ophthalmologe* 2004;101:370-6.

30. Bender R. Calculating confidence intervals for the number needed to treat. *Control Clin Trials* 2001;22:102-10.

31. Bergman L, Seregard S, Nilsson B, Lundell G, Ringborg U, Ragnarsson-Olding B. Uveal melanoma survival in Sweden from 1960 to 1998. *Invest Ophthalmol Vis Sci* 2003;44:3282-7.

32. Bergman L, Seregard S, Nilsson B, Ringborg U, Lundell G, Ragnarsson-Olding B. Incidence of uveal melanoma in Sweden from 1960 to 1998. *Invest Ophthalmol Vis Sci* 2002;43:2579-83.

33. Bornfeld N, Talies S, Anastassiou G, Schilling H, Schuler A, Horstmann GA. [Endoscopic resection of malignant melanomas of the uvea after preoperative stereotactic single dose convergence irradiation with the Leksell gamma knife]. *Ophthalmologe* 2002;99:338-44.

34. Borruat FX, Schatz NJ, Glaser JS, Feun LG, Matos L. Visual recovery from radiation-induced optic neuropathy. The role of hyperbaric oxygen therapy. *J Clin Neuroophthalmol* 1993;13:98-101.

35. Brieden SR, Schmidt J, Kroll P. [Exudative retinal detachment surgery. A prognostic++ parameter of malignant melanoma in brachytherapy?]. [German]. *Ophthalmologe* 1999.

36. Brown GC, Shields JA, Sanborn G, Augsburger JJ, Savino PJ, Schatz NJ. Radiation optic neuropathy. *Ophthalmology* 1982;89:1489-93.

37. Brown GC, Shields JA, Sanborn G, Augsburger JJ, Savino PJ, Schatz NJ. Radiation retinopathy. *Ophthalmology* 1982;89:1494-501.

38. Busse H, Muller RP. Techniques and results of 106Ru/106Rh radiation of choroidal tumours. *Trans Ophthalmol Soc U K* 1983;103:72-7.

39. Call NB, Welham RA. Epiphora after irradiation of medial eyelid tumors. *Am J Ophthalmol* 1981;92:842-5.

40. Callender GR. Malignant melanocytic tumors of the eye. A study of histologic types in 111 cases. *Trans Am Acad Ophthalmol Otolaryngol* 1931;36:131-40.

41. Caplan RJ, Pajak TF, Cox JD. Analysis of the probability and risk of cause-specific failure. *Int J Radiat Oncol Biol Phys* 1994;29:1183-6.

42. Cappin JM. Malignant melanoma and rubeosis iridis. Histopathological and statistical study. *Br J Ophthalmol* 1973;57:815-24.

43. Chappell R. Re: Caplan et al. IJROBP 29:1183-1186; 1994, and Bentzen et al. IJROBP 32:1531-1534; 1995. *Int J Radiat Oncol Biol Phys* 1996;36:988-9.

44. Char DH. Metastatic choroidal melanoma. *Am J Ophthalmol* 1978;86:76-80.

45. Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. *Am J Ophthalmol* 2003;136:180-2.

46. Char DH, Castro JR, Quivey JM, Chen GT, Lyman JT, Stone RD et al. Helium ion charged particle therapy for choroidal melanoma. *Ophthalmology* 1980;87:565-70.

47. Char DH, Castro JR, Quivey JM, Phillips TL, Irvine AR, Stone RD et al. Uveal melanoma radiation. 125I brachytherapy versus helium ion irradiation. *Ophthalmology* 1989;96:1708-15.

48. Char DH, Kroll S, Phillips TL. Uveal melanoma. Growth rate and prognosis. *Arch Ophthalmol* 1997;115:1014-8.

49. Char DH, Kroll S, Quivey JM, Castro J. Long term visual outcome of radiated uveal melanomas in eyes eligible for randomisation to enucleation versus brachytherapy. *Br J Ophthalmol* 1996;80:117-24.

50. Char DH, Kroll SM, Castro J. Long-term follow-up after uveal melanoma charged particle therapy. *Trans Am Ophthalmol Soc* 1997;95:171-87discussion.

51. Char DH, Kroll SM, Castro J. Ten-Year Follow-Up Of Helium Ion Therapy For Uveal Melanoma. *Am J Ophthalmol* 1998;125:81-9.

52. Char DH, Lonn LI, Margolis LW. Complications of cobalt plaque therapy of choroidal malanomas. *Am J Ophthalmol* 1977;84:536-41.

53. Char DH, Miller T, Crawford JB. Analysis of melanoma cell type in uveal melanoma following treatment failure. *Am J Ophthalmol* 2004;138:543-6.

54. Char DH, Miller TR, Ljung BM, Howes EJ, Stoloff A. Fine needle aspiration biopsy in uveal melanoma. *Acta Cytologica* 1989;33:599-605.

55. Char DH, Quivey JM, Castro JR, Kroll S, Phillips T. Helium ions versus iodine 125 brachytherapy in the management of uveal melanoma. A prospective, randomized, dynamically balanced trial. *Ophthalmology* 1993;100:1547-54.

56. Cleves M. Analysis of multiple failure-time data with Stata. *Stata Technical Bulletin* 1999.

57. Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma I: characteristics of patients enrolled and not enrolled. COMS report no. 9. *Am J Ophthalmol* 1998;125:767-78.

58. Collaborative Ocular Melanoma Study Group. Comparison of clinical, echographic, and histopathological measurements from eyes with medium-sized choroidal melanoma in the collaborative ocular melanoma study: COMS report no. 21. *Arch Ophthalmol* 2003;121:1163-71.

59. Coupland SE, Sidiki S, Clark BJ, McClaren K, Kyle P, Lee WR. Metastatic choroidal melanoma to the contralateral orbit 40 years after enucleation. *Arch Ophthalmol* 1996;114:751-6.

60. Cruess AF, Augsburger JJ, Shields JA, Donoso LA, Amsel J. Visual results following cobalt plaque radiotherapy for posterior uveal melanomas. *Ophthalmology* 1984;91:131-6.

61. Daftari I, Aghaian E, O'Brien JM, Dillon W, Phillips TL. 3D MRI-based tumor delineation of ocular melanoma and its comparison with conventional techniques. *Med Phys* 2005;32:3355-62.

62. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515-28.

63. Damato B. Adjunctive plaque radiotherapy after local resection of uveal melanoma. *Front Radiat Ther Oncol* 1997;30:123-32.

64. Damato B. Disease and "dis-ease" in patients with uveal melanoma. *Br J Ophthalmol* 2000;84:343-4.

65. Damato B. Time to treatment of uveal melanoma in the United Kingdom. *Eye* 2001;15:155-8.

66. Damato B, Groenewald C, McGalliard J, Wong D. Endoresection of choroidal melanoma. *Br J Ophthalmol* 1998;82:213-8.

67. Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. *Ophthalmology* 2004;111:977-83.

68. Damato BE. An approach to the management of patients with uveal melanoma. *Eye* 1993;7:388-97.

69. Damato BE. Local resection of uveal melanoma. *Bull Soc Belge Ophtalmol* 1993;248:11-7.

70. Damato BE, Paul J, Foulds WS. Predictive factors of visual outcome after local resection of choroidal melanoma. *Br J Ophthalmol* 1993;77:616-23.

71. Damato BE, Paul J, Foulds WS. Risk factors for residual and recurrent uveal melanoma after trans-scleral local resection. *Br J Ophthalmol* 1996;80:102-8.

72. De Potter P, Jamart J. Adjuvant indocyanine green in transpupillary thermotherapy for choroidal melanoma. *Ophthalmology* 2003;110:406-13.

73. De Potter P, Shields CL, Shields JA, Cater JR, Brady LW. Plaque radiotherapy for juxtapapillary choroidal melanoma. Visual acuity and survival outcome. *Arch Ophthalmol* 1996;114:1357-65.

74. Demirci H, Shields CL, Shields JA, Honavar SG, Eagle RC, Jr. Ring melanoma of the ciliary body: report on twenty-three patients. *Retina* 2002;22:698-706.

75. Detorakis ET, Engstrom RE, Jr., Wallace R, Straatsma BR. Iris and anterior chamber angle neovascularization after iodine 125 brachytherapy for uveal melanoma. *Ophthalmology* 2005;112:505-10.

76. Diener-West M, Earle JD, Fine SL, Hawkins BS, Moy CS, Reynolds SM et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. *Arch Ophthalmol* 2001;119:969-82.

77. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol* 1992;110:245-50.

78. Egan KM, Gragoudas ES, Seddon JM, Glynn RJ, Munzenreider JE, Goitein M et al. The risk of enucleation after proton beam irradiation of uveal melanoma. *Ophthalmology* 1989;96:1377-82.

79. Egan KM, Ryan LM, Gragoudas ES. Survival implications of enucleation after definitive radiotherapy for choroidal melanoma: an example of regression on time-dependent covariates. *Arch Ophthalmol* 1998.

80. Egan KM, Seddon JM, Glynn RJ, Gragoudas ES, Albert DM. Epidemiologic aspects of uveal melanoma. *Surv Ophthalmol* 1988;32:239-51.

81. Egger E, Schalenbourg A, Zografos L, Bercher L, Boehringer T, Chamot L et al. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. *Int J Radiat Oncol Biol Phys* 2001;51:138-47.

82. Eide N. Primary laser photocoagulation of "small" choroidal melanomas. *Acta Ophthalmol Scand* 1999;77:351-4.

83. Einhorn LH, Burgess MA, Gottlieb JA. Metastatic patterns of choroidal melanoma. *Cancer* 1974;34:1001-4.

84. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. *Int J Cancer* 1997;73:198-203.

85. Escalona-Benz E, Benz MS, Briggs JW, Budenz DL, Parrish RK, Murray TG. Uveal melanoma presenting as acute angle-closure glaucoma: report of two cases. *Am J Ophthalmol* 2003;136:756-8.

86. Eskelin S, Kivela T. Mode of presentation and time to treatment of uveal melanoma in Finland. *Br J Ophthalmol* 2002;86:333-8.

87. Eskelin S, Pyrhönen S, Hahka-Kemppinen M, Tuomaala S, Kivelä T. A prognostic model and staging for metastatic uveal melanoma. *Cancer* 2003;97:465-75.

88. Eskelin S, Pyrhönen S, Summanen P, Hahka-Kemppinen M, Kivelä T. Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. *Ophthalmology* 2000;107:1443-9.

89. Eskelin S, Summanen P, Pyrhönen S, Tarkkanen A, Kivelä T. Screening for metastatic uveal melanoma revisited. *Cancer* 1999;85:1151-9.

90. Finger PT. Tumour location affects the incidence of cataract and retinopathy after ophthalmic plaque radiation therapy. *Br J Ophthalmol* 2000;84:1068-70.

91. Finger PT. Plaque radiation therapy for malignant melanoma of the iris and ciliary body. *Am J Ophthalmol* 2001;132:328-35.

92. Finger PT, Berson A, Szechter A. Palladium-103 plaque radiotherapy for choroidal melanoma: results of a 7-year study. *Ophthalmology* 1999.

93. Finger PT, Moshfeghi DM, Ho TK. Palladium 103 ophthalmic plaque radiotherapy. *Arch Ophthalmol* 1991;109:1610-3.

94. Fluhs D, Anastassiou G, Wening J, Sauerwein W, Bornfeld N. The design and the dosimetry of bi-nuclide radioactive ophthalmic applicators. *Med Phys* 2004;31:1481-8.

95. Folberg R, Augsburger JJ, Gamel JW, Shields JA, Lang WR. Fine-needle aspirates of uveal melanomas and prognosis. *Am J Ophthalmol* 1985;100:654-7.

96. Font RL, Spaulding AG, Zimmermann LE. Diffuse malignant melanoma of the uveal tract: a clinicopathologic report of 54 cases. *Transactions - American Academy of Ophthalmology & Otolaryngology* 1968;72:877-95.

97. Fontanesi J, Meyer D, Xu S, Tai D. Treatment of choroidal melanoma with I-125 plaque. *Int J Radiat Oncol Biol Phys* 1993;26:619-23.

98. Foss AJE, Whelehan I, Hungerford JL, Anderson DF, Errington RD, Kacperek A et al. Predictive factors for the development of rubeosis following proton beam radiotherapy for uveal melanoma. *Br J Ophthalmol* 1997;81:748-54.

99. Foster FS, Pavlin CJ, Harasiewicz KA, Christopher DA, Turnbull DH. Advances in ultrasound biomicroscopy. *Ultrasound Med Biol* 2000;26:1-27.

100. Foulds WS, Damato BE, Burton RL. Local resection versus enucleation in the management of choroidal melanoma. *Eye* 1987;1:676-9.

101. Fraser DJJr, Font RL. Ocular inflammation and hemorrhage as initial manifestations of uveal malignant melanoma. Incidence and prognosis. *Arch Ophthalmol* 1979;97:1311-4.

102. Fuss M, Loredo LN, Blacharski PA, Grove RI, Slater JD. Proton radiation therapy for medium and large choroidal melanoma: preservation of the eye and its functionality. *Int J Radiat Oncol Biol Phys* 2001;49:1053-9.

103. Gamel JW, McLean IW, McCurdy JB. Biologic distinctions between cure and time to death in 2892 patients with intraocular melanoma. *Cancer* 1993;71:2299-305.

104. Garcia-Arumi J, Ramsay LS, Guraya BC. Transpupillary thermotherapy for circumscribed choroidal hemangiomas. *Ophthalmology* 2000;107:351-6.

105. Gass JD. Observation of suspected choroidal and ciliary body melanomas for evidence of growth prior to enucleation. *Ophthalmology* 1980;87:523-8.

106. Gonder JR, Shields JA, Albert DM, Augsburger JJ, Lavin PT. Uveal malignant melanoma associated with ocular and oculodermal melanocytosis. *Ophthalmology* 1982;89:953-60.

107. Gooley TA, Leisenring W, Crowley J, Storer BE. Why Kaplan-Meier fails and cumulative incidence succeeds when estimating failure probabilities in the presence of competing risks. In: Crowley J. Handbook of Statistics in Clinical Oncology. New York, NY: Marcel Dekker, 2001:513-23.

108. Gragoudas E, Li W, Goitein M, Lane AM, Munzenrider JE, Egan KM. Evidence-based estimates of outcome in patients irradiated for intraocular melanoma. *Arch Ophthalmol* 2002;120:1665-71.

109. Gragoudas ES, Castro JR, Quivey JM, Lyman JT, Chen GT, Phillips TL et al. The Bragg peak of proton beams for treatment of uveal melanoma. [Review] [32 refs] Current status of clinical particle radiotherapy at Lawrence Berkeley Laboratory. *Int Ophtalmol Clin* 1980;20:123-33.

110. Gragoudas ES, Egan KM, Arrigg PG, Seddon JM, Glynn RJ, Munzenrider JE. Cataract extraction after proton beam irradiation for malignant melanoma of the eye [see comments]. *Arch Ophthalmol* 1992;110:475-9.

111. Gragoudas ES, Egan KM, Seddon JM, Glynn RJ, Walsh SM, Finn SM et al. Survival of patients with metastases from uveal melanoma. *Ophthalmology* 1991;98:383-9.

112. Gragoudas ES, Egan KM, Seddon JM, Walsh SM, Munzenrider JE. Intraocular recurrence of uveal melanoma after proton beam irradiation. *Ophthalmology* 1992;99:760-6.

113. Gragoudas ES, Egan KM, Walsh SM, Regan S, Munzenrider JE, Taratuta V. Lens changes after proton beam irradiation for uveal melanoma. *Am J Ophthalmol* 1995;119:157-64.

114. Gragoudas ES, Goitein M, Verhey L, Munzenrider J, Suit HD, Koehler A. Proton beam irradiation. An alternative to enucleation for intraocular melanomas. *Ophthalmology* 1980;87:571-81.

115. Gragoudas ES, Lane AM, Regan S, Li W, Judge HE, Munzenrider JE et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol* 2000;118:773-8.

116. Gragoudas ES, Li W, Lane AM, Munzenrider J, Egan KM. Risk factors for radiation maculopathy and papillopathy after intraocular irradiation. *Ophthalmology* 1999;106:1571-8.

117. Gragoudas ES, Seddon JM, Egan K, Glynn R, Munzenrider J, Austin SM et al. Long-term results of proton beam irradiated uveal melanomas. *Ophthalmology* 1987;94:349-53.

118. Gunduz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW. Plaque radiotherapy of uveal melanoma with predominant ciliary body involvement. *Arch Ophthalmol* 1999;117:170-7.

119. Gunduz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW. Radiation complications and tumor control after plaque radiotherapy of choroidal melanoma with macular involvement. *Am J Ophthalmol* 1999;127:579-89.

120. Gunduz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW. Radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. *Arch Ophthalmol* 1999;117:609-14.

121. Guy J, Schatz NJ. Effectiveness of hyperbaric oxygen in treating radiation injury to the optic nerves and chiasm. *Ophthalmology* 1990;97:1246-7.

122. Guyer DR, Mukai S, Egan KM, Seddon JM, Walsh SM, Gragoudas ES. Radiation maculopathy after proton beam irradiation for choroidal melanoma. *Ophthalmology* 1992;99:1278-85.

123. Hadden PW, Hiscott PS, Damato BE. Histopathology of eyes enucleated after endoresection of choroidal melanoma. *Ophthalmology* 2004;111:154-60.

124. Hair JFJr, Tatham RL, Anderson RE, Black WC. Multivariate Data Analysis, 5th ed. Upper Saddle River, NJ: Prentice-Hall, 1998.

125. Hall EJ, Brenner DJ. The dose-rate effect revisited: radiobiological considerations of importance in radiotherapy. *Int J Radiat Oncol Biol Phys* 1991;21:1403-14.

126. Hall EJ, Brenner DJ. The dose-rate effect in interstitial brachytherapy: a controversy resolved. *Br J Radiol* 1992;65:242-7.

127. Harbour JW, Ahmad S, El Bash M. Rate of resolution of exudative retinal detachment after plaque radiotherapy for uveal melanoma. *Arch Ophthalmol* 2002;120:1463-9.

128. Harbour JW, Char DH, Kroll S, Quivey JM, Castro J. Metastatic risk for distinct patterns of postirradiation local recurrence of posterior uveal melanoma. *Ophthalmology* 1997;104:1785-92.

129. Harbour JW, Meredith TA, Thompson PA, Gordon ME. Transpupillary thermotherapy versus plaque radiotherapy for suspected choroidal melanomas. *Ophthalmology* 2003;110:2207-14.

130. Hawkins BS. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. *Am J Ophthalmol* 2004;138:936-51.

131. Heikkonen J, Summanen P, Immonen I, Tommila P, Toivola H, Forss M et al. Radiotherapy of malignant melanoma of the uvea with I-125 seeds. *Acta Ophthalmol (Copenh)* 1992;70:780-5.

132. Henk JM, Whitelocke RA, Warrington AP, Bessell EM. Radiation dose to the lens and cataract formation. *Int J Radiat Oncol Biol Phys* 1993;25:815-20.

133. Hill JC, Sealy R, Shackleton D, Stannard C, Korrubel J, Hering E et al. Improved iodine-125 plaque design in the treatment of choroidal malignant melanoma. *Br J Ophthalmol* 1992;76:91-4.

134. Holly EA, Aston DA, Ahn DK, Kristiansen JJ, Char DH. Uveal melanoma, hormonal and reproductive factors in women. *Cancer Res* 1991;51:1370-2.

135. Holly EA, Aston DA, Char DH, Kristiansen JJ, Ahn DK. Uveal melanoma in relation to ultraviolet light exposure and host factors. *Cancer Res* 1990;50:5773-7.

136. Horsman DE, Sroka H, Rootman J, White VA. Monosomy 3 and isochromosome 8q in a uveal melanoma. *Cancer Genetics & Cytogenetics* 1990;45:249-53.

137. Hosmer DWJr, Lemeshow S. Applied survival analysis. Regression modeling of time to event data. New York: John Wiley & Sons, 1999.

138. Houlston RS, Damato BE. Genetic predisposition to ocular melanoma. [Review] [58 refs]. *Eye* 1999.

139. Hungerford JL. Current trends in the treatment of ocular melanoma by radiotherapy. *Clin Experiment Ophthalmol* 2003;31:8-13.

140. Hungerford JL, Foss AJ, Whelahan I, Errington RD, Kacperek A, Kongerud J. Side effects of photon and proton radiotherapy for ocular melanoma. *Front Radiat Ther Oncol* 1997;30:287-93.

141. Hykin PG, Shields CL, Shields JA, Arevalo JF. The efficacy of focal laser therapy in radiation-induced macular edema. *Ophthalmology* 1998;105:1425-9.

142. Immonen IJ, Puska P, Raitta C. Transscleral contact krypton laser cyclophotocoagulation for treatment of glaucoma. *Ophthalmology* 1994;101:876-82.

143. Jampol LM, Moy CS, Murray TG, Reynolds SM, Albert DM, Schachat AP et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. *Ophthalmology* 2002;109:2197-206.

144. Jefferies P, Clemett RS, Turner JR. Radiation hazards during cobalt 60 plaque therapy for choroidal melanoma. *Aust N Z J Ophthalmol* 1993;21:37-41.

145. Jensen OA. Malignant melanomas of the uvea in Denmark 1943-1952. A clinical, histopathological, and prognostic study. *Acta Ophthalmol (Suppl)* 1963;75:1-220.

146. Jensen OA. The "Knapp-Ronne" type of malignant melanoma of the choroid. A haemangioma-like melanoma with a typical clinical picture. So-called "preretinal malignant choroidal melanoma". *Acta Ophthalmol (Copenh)* 1976;54:41-54.

147. Jiang GL, Tucker SL, Guttenberger R, Peters LJ, Morrison WH, Garden AS et al. Radiation-induced injury to the visual pathway. *Radiother Oncol* 1994;30:17-25.

148. Jones R, Gore E, Mieler W, Murray K, Gillin M, Albano K et al. Posttreatment visual acuity in patients treated with episcleral plaque therapy for choroidal melanomas: dose and dose rate effects. *Int J Radiat Oncol Biol Phys* 2002;52:989-95.

149. Journee-De Korver JG, Keunen JE. Thermotherapy in the management of choroidal melanoma. *Prog Retin Eye Res* 2002;21:303-17.

150. Journee-De Korver JG, Oosterhuis JA, de WR, Kemme H. Histopathological findings in human choroidal melanomas after transpupillary thermotherapy. *Br J Ophthalmol* 1997;81:234-9.

151. Karlsson UL, Augsburger JJ, Shields JA, Markoe AM, Brady LW, Woodleigh R. Recurrence of posterior uveal melanoma after 60Co episcleral plaque therapy. *Ophthalmology* 1989;96:382-8.

152. Kath R, Hayungs J, Bornfeld N, Sauerwein W, Hoffken K, Seeber S. Prognosis and treatment of disseminated uveal melanoma. *Cancer* 1993;72:2219-23.

153. Kellner U, Bornfeld N, Foerster MH. Radiation-induced optic neuropathy following brachytherapy of uveal melanomas. *Graefes Arch Clin Exp Ophthalmol* 1993;231:267-70.

154. Kepka AG, Johnson PM, Kline RW. The generalized geometry of eye plaque therapy. *Med Phys* 1988;15:375-9.

155. Kim MK, Char DH, Castro JL, Saunders WM, Chen GT, Stone RD. Neovascular glaucoma after helium ion irradiation for uveal melanoma. *Ophthalmology* 1986;93:189-93.

156. Kinnaert E, Morandini R, Simon S, Hill HZ, Ghanem G, Van Houtte P. The degree of pigmentation modulates the radiosensitivity of human melanoma cells. *Radiation Research* 2000;154:497-502.

157. Kinyoun JL, Chittum ME, Wells CG. Photocoagulation treatment of radiation retinopathy. *Am J Ophthalmol* 1988;105:470-8.

158. Kivelä T, Puusaari I, Damato B. Transscleral resection vs. iodine brachytherapy for choroidal malignant melanomas 6 millimeters or more in thickness: a matched case-control study. *Ophthalmology* 2003;110:2235-44.

159. Kivelä T, Eskelin S, Mäkitie T, Summanen P. Exudative retinal detachment from malignant uveal melanoma: predictors and prognostic significance. *Invest Ophthalmol Vis Sci* 2001;42:2085-93.

160. Kivelä T, Summanen P. Retinoinvasive malignant melanoma of the uvea. *Br J Ophthalmol* 1997;81:691-7.

161. Kleineidam M, Augsburger JJ, Hernandez C, Glennon P, Brady LW. Cataractogenesis after Cobalt-60 eye plaque radiotherapy [see comments]. *Int J Radiat Oncol Biol Phys* 1993;26:625-30.

162. Knutsen S, Hafslund R, Monge OR, Valen H, Muren LP, Rekstad BL et al. Dosimetric verification of a dedicated 3D treatment planning system for episcleral plaque therapy. *Int J Radiat Oncol Biol Phys* 2001;51:1159-66.

163. Krebs IP, Krebs W, Merriam JC, Gouras P, Jones IS. Radiation retinopathy: electron microscopy of retina and optic nerve. *Histol Histopathol* 1992;7:101-10.

164. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci* 2003;44:4651-9.

165. Langmann A, Langmann G, Unlucerci C, Haller E. [Motility disorders in brachytherapy of choroid melanomas with Ru106 applicators]. [German] Motilitatsstorungen bei der Brachytherapie von Aderhautmelanomen mit Ru106-Applikatoren. *Ophthalmologe* 1995;92:76-8.

166. Lee V, Cree IA, Hungerford JL. Ring melanoma--a rare cause of refractory glaucoma. *Br J Ophthalmol* 1999;83:194-8.

167. Levin LA, Gragoudas ES, Lessell S. Endothelial cell loss in irradiated optic nerves. *Ophthalmology*107:370-4.

168. Li W, Gragoudas ES, Egan KM. Metastatic melanoma death rates by anatomic site after proton beam irradiation for uveal melanoma. *Arch Ophthalmol* 2000;118:1066-70.

169. Li W, Judge H, Gragoudas ES, Seddon JM, Egan KM. Patterns of tumor initiation in choroidal melanoma. *Cancer Res* 2000;60:3757-60.

170. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc* 1989;84:1074-8.

171. Ling CC, Schell MC, Yorke ED, Palos BB, Kubiatowicz DO. Two-dimensional dose distribution of ^{125}I seeds. *Med Phys* 1985;12:652-5.

172. Linstadt D, Castro J, Char D, Decker M, Ahn D, Petti P et al. Long-term results of helium ion irradiation of uveal melanoma. *Int J Radiat Oncol Biol Phys* 1990;19:613-8.

173. Linstadt D, Char DH, Castro JR, Phillips TL, Quivey JM, Reimers M et al. Vision following helium ion radiotherapy of uveal melanoma: a Northern California Oncology Group study [see comments]. *Int J Radiat Oncol Biol Phys* 1988;15:347-52.

174. Lommatzsch PK. Experiences in the treatment of malignant melanoma of the choroid with 106Ru-106Rh beta-ray applicators. *Trans Ophthalmol Soc U K* 1973;93:119-32.

175. Lommatzsch PK. beta-Irradiation of choroidal melanoma with 106Ru/106Rh applicators. 16 Years' experience. *Arch Ophthalmol* 1983;101:713-7.

176. Lommatzsch PK, Alberti W, Lommatzsch R, Rohrwacher F. Radiation effects on the optic nerve observed after brachytherapy of choroidal melanomas with 106Ru/106Rh plaques. *Graefes Arch Clin Exp Ophthalmol* 1994;232:482-7.

177. Lumbroso L, Doz F, Urbieta M, Levy C, Bours D, Asselain B et al. Chemothermotherapy in the management of retinoblastoma. *Ophthalmology* 2002;109:1130-6.

178. Lund OE. Changes in choroidal tumors after light coagulation (and diathermy coagulation). *Arch Ophthalmol* 1966;75:458-66.

179. MacFaul PA, Bedford MA. Ocular complications after therapeutic irradiation. *Br J Ophthalmol* 1970;54:237-47.

180. Manschot WA, van Strik R. Uveal melanoma: therapeutic consequences of doubling times and irradiation results; a review. *Int Ophthalmol* 1992;16:91-9.

181. Marchini G, Gerosa M, Piovan E, Pasoli A, Babighian S, Rigotti M et al. Gamma Knife stereotactic radiosurgery for uveal melanoma: clinical results after 2 years. *Stereotact Funct Neurosurg* 1996;66 Suppl 1:208-13.

182. Margo CE, Mulla Z, Billiris K. Incidence of surgically treated uveal melanoma by race and ethnicity. *Ophthalmology* 1998;105:1087-90.

183. Marigo FA, Finger PT. Anterior segment tumors: current concepts and innovations. *Surv Ophthalmol* 2003;48:569-93.

184. Marigo FA, Finger PT, McCormick SA, Iezzi R, Esaki K, Ishikawa H et al. Iris and ciliary body melanomas: ultrasound biomicroscopy with histopathologic correlation. *Arch Ophthalmol* 2000;118:1515-21.

185. McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. *Hum Pathol* 1982;13:123-32.

186. McLean IW, Foster WD, Zimmerman LE, Gamel JW. Modifications of Callender's classification of uveal melanoma at the Armed Forces Institute of Pathology. *Am J Ophthalmol* 1983;96:502-9.

187. McLean IW, Foster WD, Zimmerman LE, Martin DG. Inferred natural history of uveal melanoma. *Invest Ophthalmol Vis Sci* 1980;19:760-70.

188. Meecham WJ, Char DH, Kroll S, Castro JR, Blakely EA. Anterior segment complications after helium ion radiation therapy for uveal melanoma. Radiation cataract. *Arch Ophthalmol* 1994;112:197-203.

189. Melia BM, Abramson DH, Albert DM, Boldt HC, Earle JD, Hanson WF et al. Collaborative Ocular Melanoma Study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years. COMS report no. 16. *Ophthalmology* 2001;108:348-66.

190. Melia M, Moy CS, Reynolds SM, Hayman JA, Murray TG, Hovland KR et al. Quality of life after iodine 125 brachytherapy vs enucleation for choroidal melanoma: 5-year results from the Collaborative Ocular Melanoma Study: COMS QOLS Report No. 3. *Arch Ophthalmol* 2006;124:226-38.

191. Merriam GR, Jr., FOCHT EF. A clinical study of radiation cataracts and the relationship to dose. *Am J Roentgenol Radium Ther Nucl Med* 1957;77:759-85.

192. Meyer-Schwickerath G, Vogel MH. Malignant melanoma of the choroid treated with photocoagulation. A 10-year follow-up. *Modern Problems in Ophthalmology* 1974;12:544-9.

193. Missotten L, Dirven W, Van der Schueren A, Leys A, De Meester G, van Limbergen E. Results of treatment of choroidal malignant melanoma with high-dose-rate strontium-90 brachytherapy. A retrospective study of 46 patients treated between 1983 and 1995. *Graefes Arch Clin Exp Ophthalmol* 1998;236:164-73.

194. Moore RF. Choroidal sarcoma treated by the intraocular insertion of radon seeds. *Br J Ophthalmol* 1930;14:145-6.

195. Mueller AJ, Bartsch DU, Folberg R, Mehaffey MG, Boldt HC, Meyer M et al. Imaging the microvasculature of choroidal melanomas with confocal indocyanine green scanning laser ophthalmoscopy. *Arch Ophthalmol* 1998;116:31-9.

196. Mueller AJ, Freeman WR, Folberg R, Bartsch DU, Scheider A, Schaller U et al. Evaluation of microvascularization pattern visibility in human choroidal melanomas: comparison of confocal fluorescein with indocyanine green angiography. *Graefes Arch Clin Exp Ophthalmol* 1999;237:448-56.

197. Mueller AJ, Freeman WR, Schaller UC, Kampik A, Folberg R. Complex microcirculation patterns detected by confocal indocyanine green angiography predict time to growth of small choroidal melanocytic tumors: MuSIC Report II. *Ophthalmology* 2002;109:2207-14.

198. Mueller AJ, Talies S, Schaller UC, Horstmann G, Wowra B, Kampik A. Stereotactic radiosurgery of large uveal melanomas with the gamma-knife. *Ophthalmology* 2000;107:1381-7.

199. Muller K, Nowak PJ, de Pan C, Marijnissen JP, Paridaens DA, Levendag P et al. Effectiveness of fractionated stereotactic radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys* 2005;63:116-22.

200. Munzenrider JE, Gragoudas ES, Seddon JM, Sisterson J, McNulty P, Birnbaum S et al. Conservative treatment of uveal melanoma: probability of eye retention after proton treatment. *Int J Radiat Oncol Biol Phys* 1988;15:553-8.

201. Nag S., Quivey J., Earle J, Followill D, Fontanesi J, Finger P et al. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. *Int J Radiat Oncol Biol Phys* 2003;56:544-55.

202. Nag S, Wang D, Wu H, Bauer CJ, Chambers RB, Davidorf FH. Custom-made "Nag" eye plaques for 125I brachytherapy. *Int J Radiat Oncol Biol Phys* 2003;56:1373-80.

203. Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. American Association of Physicists in Medicine. *Med Phys* 1995;22:209-34.

204. Nguyen QD, Foster CS. Ciliary body melanoma masquerading as chronic uveitis. *Ocul Immunol Inflamm* 1998;6:253-6.

205. Oosterhuis JA, Journee-de Korver HG, Kakebeeke-Kemme HM, Bleeker JC. Transpupillary thermotherapy in choroidal melanomas. *Arch Ophthalmol* 1995;113:315-21.

206. Oosterhuis JA, Journee-de Korver HG, Keunen JE. Transpupillary thermotherapy: results in 50 patients with choroidal melanoma. *Arch Ophthalmol* 1998;116:157-62.

207. Overgaard J, Overgaard M, Hansen PV, von der Maase H. Some factors of importance in the radiation treatment of malignant melanoma. *Radiother Oncol* 1986;5:183-92.

208. Pach JM, Robertson DM, Taney BS, Martin JA, Campbell RJ, O'Brien PC. Prognostic factors in choroidal and ciliary body melanomas with extrascleral extension. *Am J Ophthalmol* 1986;101:325-31.

209. Packer K. Verification of ophthalmic brachytherapy treatment planning. *Australas Phys Eng Sci Med* 2001;24:177-80.

210. Packer S, Rotman M. Radiotherapy of choroidal melanoma with iodine 125. [Review] [28 refs]. *Int Ophtalmol Clin* 1980;20:135-42.

211. Packer S, Rotman M, Fairchild RG, Albert DM, Atkins HL, Chan B. Irradiation of choroidal melanoma with iodine 125 ophthalmic plaque. *Arch Ophthalmol* 1980;98:1453-7.

212. Packer S, Stoller S, Lesser ML, Mandel FS, Finger PT. Long-term results of iodine 125 irradiation of uveal melanoma. *Ophthalmology* 1992;99:767-73.

213. Pane AR, Hirst LW. Ultraviolet light exposure as a risk factor for ocular melanoma in Queensland, Australia. *Ophthalmic Epidemiol* 2000;7:159-67.

214. Parmar MKB, Machin D. Survival Analysis. A Practical Approach. Chichester, NY: John Wiley & Sons, 1995.

215. Peyman GA, Juarez CP, Diamond JG, Raichand M. Ten years experience with eye wall resection for uveal malignant melanomas. *Ophthalmology* 1984;91:1720-5.

216. Peyman GA, Raichand M. Full-thickness eye wall resection of choroidal neoplasms. *Ophthalmology* 1979;86:1024-36.

217. Potter R, Janssen K, Prott FJ, Widder J, Haverkamp U, Busse H et al. Ruthenium-106 eye plaque brachytherapy in the conservative treatment of uveal melanoma: evaluation of 175 patients treated with 150 Gy from 1981-1989. *Front Radiat Ther Oncol* 1997;30:143-9.

218. Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jockel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. *Lancet* 1996;347:1222-5.

219. Quivey JM, Augsburger J, Snelling L, Brady LW. ^{125}I plaque therapy for uveal melanoma. Analysis of the impact of time and dose factors on local control. *Cancer* 1996;77:2356-62.

220. Quivey JM, Char DH, Phillips TL, Weaver KA, Castro JR, Kroll SM. High intensity 125-iodine (^{125}I) plaque treatment of uveal melanoma. *Int J Radiat Oncol Biol Phys* 1993;26:613-8.

221. Radtke ND, Augsburger JJ, Schmitt T. Management of exudative retinal detachment after plaque therapy for intraocular melanoma [letter]. *Am J Ophthalmol* 1991;112:92-4.

222. Raivio I. Uveal melanoma in Finland. An epidemiological, clinical, histological and prognostic study. *Acta Ophthalmol (Suppl)* 1977;1-64.

223. Raivio VE, Vesaluoma MH, Tervo TM, Immonen IJ, Puska PM. Corneal innervation, corneal mechanical sensitivity, and tear fluid secretion after transscleral contact 670-nm diode laser cyclophotocoagulation. *J Glaucoma* 2002;11:446-53.

224. Rajpal S, Moore R, Karakousis CP. Survival in metastatic uveal melanoma. *Cancer* 1983;52:334-6.

225. Rapizzi E, Grizzard WS, Capone AJ. Transpupillary thermotherapy in the management of circumscribed choroidal hemangioma. *Am J Ophthalmol* 1999.

226. Recsan Z, Karlinger K, Fodor M, Zalatnai A, Papp M, Salacz G. MRI for the evaluation of scleral invasion and extrascleral extension of uveal melanomas. *Clin Radiol* 2002;57:371-6.

227. Robertson DM. Changing concepts in the management of choroidal melanoma. *Am J Ophthalmol* 2003;136:161-70.

228. Robertson DM, Buettner H, Bennett SR. Transpupillary thermotherapy as primary treatment for small choroidal melanomas. *Arch Ophthalmol* 1999;117:1512-9.

229. Robertson DM, Earle J, Anderson JA. Preliminary observations regarding the use of iodine-125 in the management of choroidal melanoma. *Trans Ophthalmol Soc U K* 1983;103:155-60.

230. Rohrbach JM, Steuhl KP, Kreissig I, Thiel HJ. Epidemiologie, Invasion und Wachstum nicht-iridaler Aderhautmelanome und assoziierte intraokulare Veränderungen: Histologische Untersuchung von 223 Augen. *Klin Monatsbl Augenheilkd* 1990;197:455-65.

231. Rotman M, Long RS, Packer S, Moroson H, Galin MA, Chan B. Radiation therapy of choroidal melanoma. *Trans Ophthalmol Soc U K* 1977;97:431-5.

232. Saornil MA, Egan KM, Gragoudas ES, Seddon JM, Walsh SM, Albert DM. Histopathology of proton beam-irradiated vs enucleated uveal melanomas. *Arch Ophthalmol* 1992;110:1112-8.

233. Schenken LL, Hagemann RF. Time/dose relationship in experimental radiation cataractogenesis. *Radiology* 1975;117:193-8.

234. Schilling H, Bornfeld N, Friedrichs W, Pauleikhoff D, Sauerwein W, Wessing A. Histopathologic findings in large uveal melanomas after brachytherapy with iodine 125 ophthalmic plaques. *Germ J Ophthalmol* 1994;3:232-8.

235. Schmittel A, Bechrakis NE, Martus P, Mutlu D, Scheibenbogen C, Bornfeld N et al. Independent prognostic factors for distant metastases and survival in patients with primary uveal melanoma. *Eur J Cancer* 2004;40:2389-95.

236. Scholes AG, Damato BE, Nunn J, Hiscott P, Grierson I, Field JK. Monosomy 3 in uveal melanoma: correlation with clinical and histologic predictors of survival. *Invest Ophthalmol Vis Sci* 2003;44:1008-11.

237. Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. *Arch Ophthalmol* 1983;101:1894-9.

238. Seddon JM, Gragoudas ES, Albert DM, Hsieh CC, Polivogianis L, Friedenberg GR. Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation. *Am J Ophthalmol* 1985;99:282-90.

239. Seddon JM, Gragoudas ES, Egan KM, Glynn RJ, Howard S, Fante RG et al. Relative survival rates after alternative therapies for uveal melanoma. *Ophthalmology* 1990;97:769-77.

240. Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH. Host factors, UV radiation, and risk of uveal melanoma. A case-control study. *Arch Ophthalmol* 1990;108:1274-80.

241. Seddon JM, Gragoudas ES, Polivogianis L, Hsieh CC, Egan KM, Goitein M et al. Visual outcome after proton beam irradiation of uveal melanoma. *Ophthalmology* 1986;93:666-74.

242. Sener EC, Kiratli H, Gedik S, Sanac AS. Ocular motility disturbances after episcleral plaque brachytherapy for uveal melanoma. *J AAPOS* 2004;8:38-45.

243. Seregard S. Long-term survival after ruthenium plaque radiotherapy for uveal melanoma. A meta-analysis of studies including 1,066 patients. *Acta Ophthalmologica Scandinavica* 1995;77:414-7.

244. Seregard S, Landau I. Transpupillary thermotherapy as an adjunct to ruthenium plaque radiotherapy for choroidal melanoma. *Acta Ophthalmol Scand* 2001;79:19-22.

245. Shammas HF, Blodi FC. Orbital extension of Choroidal and ciliary body melanomas. *Arch Ophthalmol* 1977;95:2002-5.

246. Shammas HF, Blodi FC. Prognostic factors in choroidal and ciliary body melanomas. *Arch Ophthalmol* 1977;95:63-9.

247. Shields CL, Cater J, Shields JA, Singh AD, Santos MCM, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol* 2000;118:360-4.

248. Shields CL, Demirci H, Dai V, Marr BP, Mashayekhi A, Materin MA et al. Intravitreal triamcinolone acetonide for radiation maculopathy after plaque radiotherapy for choroidal melanoma. *Retina* 2005;25:868-74.

249. Shields CL, Naseripour M, Cater J, Shields JA, Demirci H, Youseff A et al. Plaque radiotherapy for large posterior uveal melanomas (>=8-mm thick) in 354 consecutive patients. *Ophthalmology* 2002;109:1838-49.

250. Shields CL, Santos MCM, Diniz W, Gunduz K, Mercado G, Cater JR et al. Thermotherapy for retinoblastoma. *Arch Ophthalmol* 1999;117:885-93.

251. Shields CL, Shield JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. *Ophthalmology* 2002;109:225-34.

252. Shields CL, Shields JA, Cater J, Gunduz K, Miyamoto C, Micaily B et al. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. *Arch Ophthalmol* 2000;118:1219-28.

253. Shields CL, Shields JA, Cater J, Lois N, Edelstein C, Gunduz K et al. Transpupillary thermotherapy for choroidal melanoma: tumor control and visual results in 100 consecutive cases. *Ophthalmology* 1998.

254. Shields CL, Shields JA, De Potter P. Patterns of indocyanine green videoangiography of choroidal tumours. *Br J Ophthalmol* 1995;79:237-45.

255. Shields CL, Shields JA, De Potter P, Cater J, Tardio D, Barrett J. Diffuse choroidal melanoma. Clinical features predictive of metastasis. *Arch Ophthalmol* 1996;114:956-63.

256. Shields CL, Shields JA, Karlsson U, Markoe AM, Brady LW. Reasons for enucleation after plaque radiotherapy for posterior uveal melanoma. Clinical findings. *Ophthalmology* 1989;96:919-23.

257. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology* 1995;102:1351-61.

258. Shields CL, Shields JA, Shields MB, Augsburger JJ. Prevalence and mechanisms of secondary intraocular pressure elevation in eyes with intraocular tumors. *Ophthalmology* 1987;94:839-46.

259. Shields JA. Lesions simulating malignant melanoma of the posterior uvea. *Arch Ophthalmol* 1973;89:466-71.

260. Shields JA. Current approaches to the diagnosis and management of choroidal melanomas. [Review] [163 refs]. *Surv Ophthalmol* 1977;21:443-63.

261. Shields JA. Management of posterior uveal melanoma: past, present, future. *Retina* 2002;22:139-42.

262. Shields JA, Augsburger JJ, Brady LW, Day JL. Cobalt plaque therapy of posterior uveal melanomas. *Ophthalmology* 1982;89:1201-7.

263. Shields JA, Augsburger JJ, Donoso LA, Bernardino VJ, Portenar M. Hepatic metastasis and orbital recurrence of uveal melanoma after 42 years. *Am J Ophthalmol* 1985;100:666-8.

264. Shields JA, Glazer LC, Mieler WF, Shields CL, Gottlieb MS. Comparison of xenon arc and argon laser photocoagulation in the treatment of choroidal melanomas. *Am J Ophthalmol* 1990;109:647-55.

265. Shields JA, Shields CL, Donoso LA. Management of posterior uveal melanoma. *Surv Ophthalmol* 1991;36:161-95.

266. Shields JA, Shields CL, Ehya H, Eagle RCJ, De Potter P. Fine-needle aspiration biopsy of suspected intraocular tumors. The 1992 Urwick Lecture. *Ophthalmology* 1993;100:1677-84.

267. Sia S, Harper C, McAllister I, Perry A. Iodine-I25 episcleral plaque therapy in uveal melanoma. *Clin Exp Ophthalmol* 2000;28:409-13.

268. Singh AD, Damato B, Howard P, Harbour JW. Uveal melanoma: genetic aspects. *Ophthalmol Clin North Am* 2005;18:85-97, viii.

269. Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. *Ophthalmology* 2005;112:1784-9.

270. Singh AD, Rennie IG, Kivela T, Seregard S, Grossniklaus H. The Zimmerman-McLean-Foster hypothesis: 25 years later. *Br J Ophthalmol* 2004;88:962-7.

271. Singh AD, Rennie IG, Seregard S, Giblin M, McKenzie J. Sunlight exposure and pathogenesis of uveal melanoma. *Surv Ophthalmol* 2004;49:419-28.

272. Singh AD, Shields CL, Shields JA, De Potter P. Bilateral primary uveal melanoma. Bad luck or bad genes? *Ophthalmology* 1996;103:256-62.

273. Singh AD, Shields CL, Shields JA, Sato T. Uveal melanoma in young patients. *Arch Ophthalmol* 2000;118:918-23.

274. Singh AD, Topham A. Incidence of uveal melanoma in the United States: 1973-1997. *Ophthalmology* 2003;110:956-61.

275. Singh AD, Wang MX, Donoso LA, Shields CL, De Potter P, Shields JA. Genetic aspects of uveal melanoma: a brief review. [Review] [45 refs]. *Semin Oncol* 1996;23:768-72.

276. Sobin LH, Wittekind Ch. TNM Classification of Malignant Tumours, 5th ed. New York: J. Wiley & Sons, Inc., 1997.

277. Sobin LH, Wittekind Ch. TNM Classification of Malignant Tumours, 6th ed. New York: Wiley-Liss, 2002.

278. Soulieres D, Rousseau A, Tardif M, Larochelle M, Tremblay M, Vaillancourt L et al. The radiosensitivity of uveal melanoma cells and the cell survival curve. *Graefes Arch Clin Exp Ophthalmol* 1995;233:85-9.

279. Spencer WH. Optic nerve extension of intraocular neoplasms. *Am J Ophthalmol* 1975;80:465-71.

280. Spencer WH, Iverson HA. Diffuse melanoma of the iris, with extrabulbar extension via the optic nerve. *Surv Ophthalmol* 1965;10:365-71.

281. Stallard HB. Radiotherapy for malignant melanoma of the choroid. *Br J Ophthalmol* 1966;50:147-55.

282. Straatsma BR, Fine SL, Earle JD, Hawkins BS, Diener-West M, McLaughlin JA. Enucleation versus plaque irradiation for choroidal melanoma. *Ophthalmology* 1988;95:1000-4.

283. Summanen P, Immonen I, Heikkonen J, Tommila P, Laatikainen L, Tarkkanen A. Survival of patients and metastatic and local recurrent tumor growth in malignant melanoma of the uvea after ruthenium plaque radiotherapy. *Ophthalmic Surg* 1993;24:82-90.

284. Summanen P, Immonen I, Kivelä T, Tommila P, Heikkonen J, Tarkkanen A. Visual outcome of eyes with malignant melanoma of the uvea after ruthenium plaque radiotherapy. *Ophthalmic Surg Lasers* 1995;26:449-60.

285. Summanen P, Immonen I, Kivelä T, Tommila P, Heikkonen J, Tarkkanen A. Radiation related complications after ruthenium plaque radiotherapy of uveal melanoma. *Br J Ophthalmol* 1996;80:732-9.

286. Summanen P, Teppo L, Kivelä T, Laatikainen L, Tarkkanen A. Incidence of malignant uveal melanoma in the Finnish population. *XIth Congress of the European Society of Ophthalmology: Final Programme and Abstract Book* 1997;262.

287. Swerdlow AJ. Epidemiology of eye cancer in adults in England and Wales, 1962-1977. *Am J Epidemiol* 1983;118:294-300.

288. Tarkkanen A, Laatikainen L. Fluorescein angiography in the long-term follow-up of choroidal melanoma after conservative treatment. *Acta Ophthalmol (Copenh)* 1985;63:73-9.

289. Teikari JM, Raivio I. Incidence of choroidal malignant melanoma in Finland in the years 1973-1980. *Acta Ophthalmol (Copenh)* 1985;63:661-5.

290. The Collaborative Ocular Melanoma Study Group. Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. *Arch Ophthalmol* 1990;108:1268-73.

291. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. *Arch Ophthalmol* 1997;115:1537-44.

292. The Collaborative Ocular Melanoma Study Group. Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol* 1997;115:886-93.

293. The Collaborative Ocular Melanoma Study Group. Histopathologic characteristics of uveal melanomas in eyes enucleated from the Collaborative Ocular Melanoma Study. COMS report no. 6. *Am J Ophthalmol* 1998;125:745-66.

294. The Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma II: initial mortality findings. COMS report no. 10. *Am J Ophthalmol* 1998;125:779-96.

295. The Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma III: local complications and observations following enucleation COMS report no. 11. *Am J Ophthalmol* 1998;126:362-72.

296. The Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol* 2001;119:670-6.

297. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer, 2000.

298. Tuomaala S, Eskelin S, Tarkkanen A, Kivela T. Population-based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. *Invest Ophthalmol Vis Sci* 2002;43:3399-408.

299. Valcarcel F, Valverde S, Cardenes H, Cajigal C, De la Torre A, Magallon R et al. Episcleral iridium-192 wire therapy for choroidal melanomas. *Int J Radiat Oncol Biol Phys* 1994;30:1091-7.

300. van den Aardweg GJ, Kilic E, de Klein A, Luyten GP. Dose fractionation effects in primary and metastatic human uveal melanoma cell lines. *Invest Ophthalmol Vis Sci* 2003;44:4660-4.

301. van den Aardweg GJ, Naus NC, Verhoeven AC, de Klein A, Luyten GP. Cellular radiosensitivity of primary and metastatic human uveal melanoma cell lines. *Invest Ophthalmol Vis Sci* 2002;43:2561-5.

302. van Ginderdeuren R, van Limbergen E, Spileers W. 18 years' experience with high dose rate strontium-90 brachytherapy of small to medium sized posterior uveal melanoma. *Br J Ophthalmol* 2005;89:1306-10.

303. Viebahn M, Barricks ME, Osterloh MD. Synergism between diabetic and radiation retinopathy: case report and review. *Br J Ophthalmol* 1991;75:629-32.

304. Vogel MH. Treatment of malignant choroidal melanomas with photocoagulation. Evaluation of 10-year follow-up data. *Am J Ophthalmol* 1972;74:1-11.

305. Vrabec TR, Augsburger JJ, Gamel JW, Brady LW, Hernandez C, Woodleigh R. Impact of local tumor relapse on patient survival after cobalt 60 plaque radiotherapy. *Ophthalmology* 1991;98:984-8.

306. Wachtlin J, Bechrakis NE, Schueler AO, Helbig H, Bornfeld N, Foerster MH. Phacoemulsification following treatment of choroidal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2000;238:942-8.

307. Wagoner MD, Albert DM. The incidence of metastases from untreated ciliary body and choroidal melanoma. *Arch Ophthalmol* 1982;100:939-40.

308. Wara WM, Irvine AR, Neger RE, Howes EL, Jr., Phillips TL. Radiation retinopathy. *Int J Radiat Oncol Biol Phys* 1979;5:81-3.

309. Warren RM. Prognosis of malignant melanomas of the choroid and ciliary body. *Curr Concepts Ophthalmol* 1974;4:158-66.

310. Weaver KA. The dosimetry of ^{125}I seed eye plaques. *Med Phys* 1986;13:78-83.

311. Weber DC, Bogner J, Verwey J, Georg D, Dieckmann K, Escude L et al. Proton beam radiotherapy versus fractionated stereotactic radiotherapy for uveal melanomas: A comparative study. *Int J Radiat Oncol Biol Phys* 2005;63:373-84.

312. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. *Ophthalmology* 1999;106:1579-87.

313. Win PH, Robertson DM, Buettner H, McCannel CA, Bennett SR. Extended follow-up of small melanocytic choroidal tumors treated with transpupillary thermotherapy. *Arch Ophthalmol* 2006;124:503-6.

314. Wycliffe ND, Mafee MF. Magnetic resonance imaging in ocular pathology. *Top Magn Reson Imaging* 1999;10:384-400.

315. Yang CM, Olsen KR, Schwade JG, Houdek PV, Markoe AM, Pisciotta V et al. Dose rate effect of 125I irradiation on normal rabbit eyes and experimental choroidal melanoma. *Experimental Eye Research* 1993;57:577-85.

316. Yanoff M. Glaucoma mechanisms in ocular malignant melanomas. *Am J Ophthalmol* 1970;70:898-904.

317. Yanoff M, Fine BS. Ocular Pathology, 4th ed. London: Mosby-Wolfe, 1996.

318. Zimmerman LE. Malignant melanoma. In: Spencer WH. Ophthalmic Pathology, 3 ed. Philadelphia: W.B. Saunders Company, 1986:2072-139.

319. Zimmerman LE, McLean IW. An evaluation of enucleation in the management of uveal melanomas. [Review] [98 refs]. *Int Ophtalmol Clin* 1980;20:1-31.

320. Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells. *Br J Ophthalmol* 1978;62:420-5.